THE

AMERICAN JOURNAL

OF THE

MEDICAL SCIENCES

E. B. KRUMBHAAR, M.D.

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ACTING ASSISTANT EDITOR

NEW SERIES

VOL. 206

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PROGRESS OF MEDICAL SCIENCE

ORIGINAL ARTICLES

ATYPICAL PERNICIOUS ANEMIA OF YOUNG ADULTS

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In spite of its relative infrequency, pernicious anemia has received an unusual amount of attention in the past 15 years. This is due primarily to the discovery of the specificity of liver therapy in this disease.[21] To the description of the disease little has been added since Addison's classic presentation in 1855,[1] and though the concept of etiology, therapy and prognosis has been revolutionized, recognition of the disease still depends on the typical history and physical findings, substantiated by the characteristic changes of the blood. When typical, pernicious anemia is one of the most easily diagnosed diseases, in part because of the common anthropologic characteristics shared by the great majority of patients.[7,13] Few diseases, indeed, can so readily be "spotted," since to the classic triad of gray hair, blue eyes and "lemon-yellow" pallor are added the round, "neutral" facies, the icterus of the scleræ, the smooth tongue, the short chest, long abdomen and spade-like hands. In addition, it is usually a disease of light-skinned, fair-haired people and occurs most commonly past the third decade. However, because of the typicalness of the great majority of cases, the atypical ones tend, only too often, to misguide us.

We have recently observed a group of cases which, though fulfilling the diagnostic criteria of achylia gastrica, typical blood and bone-marrow changes, and the specific clinical and hematologic response to liver therapy, nevertheless differed sufficiently in detail to cause diagnostic difficulties. This series, consisting of 9 women, 5 of whom were colored, all under 35 years of age, was characterized by illness of variable duration, weight loss, fever, jaundice, anemia, heart murmurs, and hepatomegaly or splenomegaly or both. In none of the cases was the diagnosis of pernicious anemia made until several other diseases had been considered and ruled out.

Illustrative Cases. CASE 3. Age 29, colored female. This patient became acutely ill with symptoms of dyspnea, palpitation, weakness, faintness, ankle

edema and epistaxes. Examination showed asthenia, pallor, icterus of the scleræ, a precordial systolic thrill, and a systolic murmur heard best over the mitral area and the base of the heart. There was moderate enlargement of the spleen and liver. The temperature was 104.2° F., pulse 124, respirations 28, blood pressure 140/60.

The diagnosis of rheumatic heart disease with mitral and aortic involvements and a superimposed subacute bacterial endocarditis was made.

Laboratory findings showed a severe anemia, red cells in the urinary sediment, a negative Kahn test, a negative blood culture, and an icterus index of 6.0. Roentgen-ray of the chest showed the heart somewhat enlarged and the hilar markings of the lung considerably increased. ECG showed a tachycardia, right ventricular preponderance, an isoelectric T^1 and a biphasic T^2.

Because of the severe anemia, liver and iron therapy were given empirically. Within a few days the fever subsided and marked subjective improvement was noted. Concurrently the anemia improved and in 4 weeks the patient was well enough to be discharged.

She was well for 6 months, then became weak and began to vomit. On reëxamination the findings were as before, except that the spleen was no longer palpable. Because of the relatively long remission the diagnosis of subacute bacterial endocarditis was placed in question and new hematologic studies were undertaken. The blood findings at this time were typical of pernicious anemia (Table 1). Subsequently the story was elicited that the tongue was "sensitive," and "tingling" had been noted in the fingers. On gastroscopic examination an atrophic gastritis was found.

This patient made an uneventful recovery on liver therapy* and has been adequately maintained on small amounts of liver.

CASE 4. Age 29, white female. This patient developed the symptoms of palpitation, dyspnea, ankle edema, backache, abdominal pain, and vomiting. Examination showed pallor, decayed teeth, coated tongue, moderate cardiac enlargement both to the right and left, a presystolic thrill and systolic and presystolic murmurs heard over the apex and transmitted to the axilla. The edge of the spleen was palpable 8 cm. below the costal margin.

TABLE 1.—SUMMARY OF THE INITIAL BLOOD FINDINGS AT VARIOUS PERIODS.

Case	R.B.C.	Hb., %	Color index	W.B.C.	Admission, retic. %	Remarks
1	0.70	15	1.0	4900	12.2	Epistaxes
2	1.91	44	.1 1	4000	1.2	
3	No record of first examination					
	0.89	18	1 0	5750	1.0	Epistaxes
4	2 94	33	0.6	5600	1.0	Epistaxes, menorrhagia
	*2.05	48	1.2	5100	29.4	
	1 34	36	1.3	4500	6.4	
5	1.01	16	0.8	6900	8.2	
	2.20	49	1.1	3400	0.4	
6	2.56	37	0.7	7150	4.2	Epistaxes, menorrhagia
7	1.23	25	1.0	4900	0.4	
8	0.73	19	1.3	2300		
	1.40	38	1.4	6600	1.4	
9	1.27	27	1.0	5450	1.4	Epistaxes, menorrhagia

* After transfusion.
Hemoglobin %—Sahli.   15.6 gm.—100%.

The diagnoses of mitral stenosis, regurgitation and sepsis lenta were made. The bone marrow was reported as showing no evidence of pernicious anemia.

The laboratory findings showed a profound hypochromic anemia (Table 1), achylia gastrica, a "doubtful" Kahn test, stools which were negative for

* Most of the liver injections were given in the prestandardization era and much of the liver used was experimental in character. It has only been since the last of 1939 that the exact unitage was ascertainable. Since that time we have been working with liver containing approximately 7 to 10 units per cc. furnished by Dr. David Klein of the Wilson Laboratories.

occult blood, negative blood cultures, and a normal icterus index. Roentgen ray of the chest showed the heart to be moderately enlarged and the hilar markings increased. Fluoroscopy of the duodenum revealed a peptic ulcer. The ECG was essentially normal.

Liver, iron, and a transfusion of 500 cc. of blood were given empirically. There was gradual improvement and a month later the patient was discharged.

She was well for a year and then again started to vomit. Dyspnea, weakness, pallor, fever, palpitation, heart consciousness and precordial pain were now all quite marked. Edema of the feet, poor appetite, and weight loss were also noted. At this time a story of "growing pains" without definite history of rheumatism was elicited. There were "sticky" feelings in the fingers. Examination showed pallor, an icteric tint of the skin and sclerae, the evidences of weight loss, graying hair, bleeding gums, a pale but otherwise normal tongue. The heart was moderately enlarged to the left and a systolic murmur was heard at the apex. The edges of both the liver and spleen were palpated 8 cm. below their respective costal margins. The liver edge was tender. There was pitting edema over the sacrum and legs. No abnormality of the reflexes was noted. The diagnosis of subacute bacterial endocarditis was again made and blood transfusions were given. Severe epistaxes followed and at times the patient was irrational. The temperature was septic in character and the patient's condition became critical. Eight days after admission the signs of mitral and aortic lesions were noted and petachiae were found. After the fourth transfusion she began to improve, became afebrile, and was discharged.
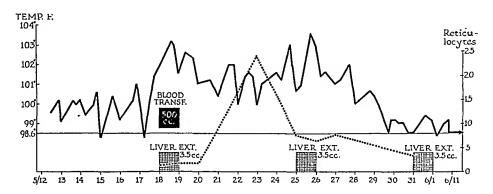
FIG. 1.—Willa Mae W. Showing febrile course and reticulocyte response during hospital stay.

Other findings at this time were: a negative Kahn test, normal hypotonic fragility of the red cells, an icterus index of 18, evidence of "mild myocardial damage" in the ECG, an increased cardio-thoracic ratio and infiltrative changes in the lower two-thirds of the lungs in the Roentgen ray.

The patient was followed in the cardiac clinic. Because of the recurrence of fever, weakness and gnawing pains in the left side of the abdomen, she was readmitted to the hospital 3 months later. Her menstrual periods had now become more profuse and large clots were passed. Epistaxes recurred. The ankles were swollen, the skin and mucous membranes slightly jaundiced, the heart was enlarged and a systolic thrill was felt at the apex. The spleen was still readily palpable and quite hard. Because of the protracted course, repeatedly negative blood cultures and the finding of glands in the axillae at this time, Hodgkin's disease was added to the diagnostic possibilities. Bone-marrow biopsy was again performed and the marrow was found to be *hypoplastic;* the white cells outnumbered the nucleated reds 3 to 1; many very primitive red cells were found and the red cell development appeared megaloblastic. Maturation of the white cells also appeared abnormal. Because of the megaloblastic maturation of the red cells and the atypical nature of the white cells a "liver extract deficiency" was suggested. Intramuscular liver therapy

was begun and the patient recovered without any additional therapy. The temperature, which had been as high as 104° F. on admission, subsided following the administration of liver. An axillary lymph node removed for biopsy showed non-specific hyperplasia. The liver and spleen gradually diminished in size and the heart murmurs disappeared.
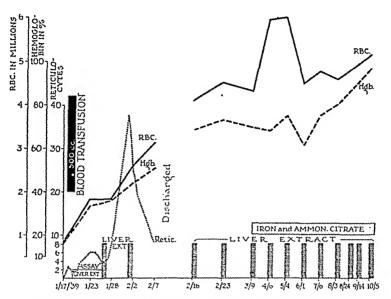
FIG. 2.—Sadie C. Showing specific response to liver therapy with subsequent development of "iron deficiency."
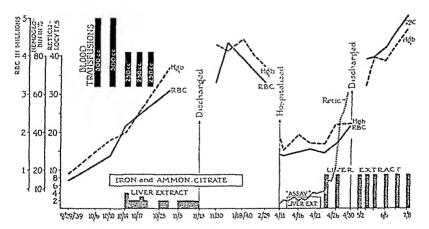
FIG. 3.—Christine P. Showing therapeutically induced remissions and spontaneous relapse.

Since leaving the hospital her course has been uneventful and she has been very well maintained on small amounts of parenteral liver extract for 3½ years.

CASE 8. Age 17, white female. In this patient, the symptoms of edema of the legs, weakness, anorexia, dyspnea, facial edema, and occasional precordial pain[35] developed acutely. Examination showed an acutely ill girl with marked pallor, fever of 103.6° F., pulse of 126, edema of the face, puffy eyelids, and pale conjunctivæ. There was moderate enlargement of the heart to both right

and left, with systolic and mid-diastolic murmurs and the suggestion of a thrill over the apex. The liver was palpable 4 cm. below the costal margin. There was pitting edema of the ankles. The spleen was not palpable on admission but 2 days later was reported enlarged to percussion and 2 weeks later it became palpable.

Diagnoses considered were: (1) acute rheumatic fever, (2) subacute glomerulonephritis, (3) aplastic anemia, (4) hemolytic anemia, (5) aleukemic leukemia, and (6) primary "splenic anemia."

The laboratory data showed a severe macrocytic anemia (Table 1), and achylia gastrica. The sternal marrow was *hypocellular*. Red cell maturation was *normoblastic* in type and the white cells appeared to be essentially normal. Gastroscopy showed an extensive atrophic gastritis.

Blood transfusions, liver extract, iron and dilute hydrochloric acid were given. She gradually improved (Fig. 3) and was discharged in 6 weeks.

In the out-patient clinic the course was progressively downhill. In 6 months the picture had changed considerably. At this time in addition to the weakness there was moderate jaundice, a smooth tongue, pallor, slight icterus of the scleræ and the liver was still 4 cm. below the costal margin though the spleen could no longer be palpated. The changes in the blood were at this time characteristic of pernicious anemia. The marrow was now typical of pernicious anemia in relapse. On intramuscular liver therapy she recovered uneventfully (Fig. 3).

Since her discharge from the hospital 3 years ago she has been well maintained on parenteral liver therapy excepting when, because of irregularity of attendance, slight relapses have occurred.

TABLE 2.—SUMMARY OF HISTORY AND PHYSICAL FINDINGS

Cases:	1	2	3	4	5	6	7	8	9
Age (yrs.) . . .	29	31	29	29	30	26	25	17	35
Color	Colored	White	Colored	White	Colored	White	Colored	White	Colored
Duration . . .	8 mos. (2 yrs.)	2 yrs.	3 yrs.	2 yrs.	3 wks.	1 yr.	1 yr.	1 wk.	1 mo
Illness	Acute	Chronic	Chronic	Chronic	Acute	Chronic	Chronic	Acute	Acute
Nourishment . .	Adeq.	Adeq.	?	Poor	Emac.	Adeq.	Thin	Adeq.	Adeq.
Weight loss . .	19 lbs.	18 lbs.- 1 yr.	8–10 lbs.- 1 yr.	Marked	?	?	25 lbs.- 8 mos.	?	9 lbs.
Weight gain after therapy . . .	40 lbs. in 6 mos.	26 lbs. in 6 mos.	19 lbs. in 6 mos.	?	26 lbs. in 3 mos.	17 lbs. in 8 mos.	27 lbs. in 5 mos.	?	30 lbs. in 6 mos.
Highest fever . .	104.4° F.	99.6° F.	104.2° F.	104° F.	102.6° F.	102° F.	100.4° F.	103.6° F.	103.5° F.
Pallor	Present	Present	Present	Present	Present	Present	Present	Present	?
Icterus	Present	Present	Present	Present	Present	Present	Present	Present	?
Tongue . . .	?	"Mod. atroph."	"Not smooth"	"Coated"	"Smooth"	"Sides smooth"	"Smooth"	?	?
Types of murmurs	Syst. Presyst. Diast.	Syst.	Syst. Presyst.	Syst. Presyst. Diast.	Syst.	Syst.	Syst.	Syst. Mid-diast.	0
Liver (extension below costal margin	4 cm.	Not palpable	4 cm.	8 cm.	Palp. (tender)	Not palpable	"Mod. enlarged"	4 cm.	Not palpable
Spleen	Palpable	Palpable	Palpable	8 cm.	Not palpable	Palpable	Palpable	Palpable	Not palpable

Discussion. The laboratory and other data are analyzed in Tables 1 and 2. In every case presented the diagnosis of pernicious anemia was finally definitely established.* Macrocytic anemia, complete achlorhydria and a specific, favorable response to liver therapy was demonstrated at some time in all patients. When examined, the bone-marrow was megaloblastic[6] with the exceptions noted above, and the stomach showed atrophic gastritis.[27] Typical relapses occurred in 6 of the patients when liver therapy was withheld—the shortest time between relapses being $2\frac{1}{2}$ months, the longest 15 months.[31] The manifestations of the disease differed sufficiently from those of typical pernicious anemia to cause diagnostic difficulties. The most significant differences were: the occurrence in a younger age group, the frequency in negroes, the apparent acuteness of the onset, the misleading prominence of cardiac symptoms, the febrile course so strongly suggestive of infection and the marked paucity of neurologic complaints. It thus appears that the disease tends to be more severe in the younger age groups. This is substantiated by the relatively short periods between relapses. Yet the maintenance of these patients at adequate blood and clinical levels requires no more liver than that required by patients in the older age groups and in essentially the same economic strata.[22,23] It is possible that these patients will in time require more liver than those developing the disease late in life.

A striking feature of this study was the frequency with which the diagnosis of rheumatic fever and/or rheumatic heart disease was made. This happened in 7 of the 9 cases, and in 5 of these the diagnosis of subacute bacterial endocarditis was made in addition. Most of the findings of the latter condition were present and only the positive blood cultures were lacking to substantiate the diagnosis. This introduces the interesting question of how many of the "cured" or "recovered" cases of subacute bacterial endocarditis recorded in the literature and which were treated with transfusions and liver extract were in reality cases such as here reported.

We wish to emphasize the necessity of: (1) considering pernicious anemia in the differential diagnosis of any case presenting anemia, regardless of age or color, if the anemia is of a degree more marked than can *readily* be explained; and (2) the importance of making an etiologic diagnosis *before* treatment is begun.

DIFFERENTIAL DIAGNOSIS. "Secondary anemia" was diagnosed in 6 of the 9 cases. We wish to emphasize the lack of value of this term which throws no nosologic, etiologic, prognostic or therapeutic light on the underlying condition.

Rheumatic fever, with or without rheumatic carditis, was diagnosed in 8 of the 9 cases and in 5 of these a superimposed subacute bacterial endocarditis was postulated. These diagnoses were based on the history of joint pains, fever, precordial distress or palpitation with dyspnea and edema, heart murmurs, splenomegaly, anemia and occasional petechiæ. It is striking, in reviewing the records, how well simulated

* With the changing values of diagnostic criteria in the group of macrocytic anemias the diagnosis of pernicious anemia might be questioned in some of the cases, on the basis of the evidence presented. In any case they cast valuable light on such atypical cases.—EDITOR

these diseases were, and even in retrospect it is not at all surprising that these diagnoses should have been seriously entertained.

Sickle cell anemia and hemolytic anemia was diagnosed in 7 of the 9 cases, the former in 4 of 5 colored patients, the latter in 3 of the 4 white and 1 of the colored women. Basis for these diagnoses was the anemia, the jaundice and the splenomegaly. However, in no case was sickling of the cells, spherocytosis, increased hypotonic fragility, or evidences of active regeneration (reticulocytosis without therapy, leukocytosis, etc.) demonstrable. The differential diagnosis between pernicious anemia and acute hemolytic anemia may at times however be difficult, as Dameshek and Schwartz[6a] have already pointed out in a previous publication.

Aleukemic leukemia was the other diagnosis most frequently entertained and had in its favor the profound anemia, the leukopenia often with immature white cells and not infrequent nucleated red cells, the fever, the spleno- and hepatomegaly, the not infrequent nasal or vaginal bleedings and the severity and acuteness of the illness.

SYMPTOMS. The most prominent symptoms were *dyspnea* (in 7), *weakness* and *tiredness* (in 6), *palpitation, edema* and *vomiting* (in 5). The first 4 of these are the symptoms most frequently associated with pernicious anemia in relapse. Cabot[4] in his review of 1200 cases found dyspnea to have been present in 800 of 915, weakness and tiredness in 1101 of 1139, palpitation in "almost every case" and edema in 330 of 572 cases. The incidence of other complaints roughly parallels the findings of Cabot and others,[30] as well as our own experience with typical cases of pernicious anemia. The symptoms referable to the anemia and secondarily to the cardiovascular system are most prominent, while the gastro-intestinal symptoms are of secondary importance and the neurologic complaints are the mildest.

The onset of the illness was acute in 4 and insidious in 5 of our cases, and though prodromal symptoms of failing health, weakness and pallor had been present in most for varying periods of time, the disease was thought to be of less than 1 month's duration in 3 and of 8 months to a year in 3 others. The onset was acute in only 28 of Cabot's 1200 cases,[4] and it would seem from the reports in the literature[5,34] that "acute" cases of pernicious anemia are more common in those patients in whom the disease manifests itself early in life.

All the patients lost weight.[14] In the 5 who knew the amount of weight lost this varied from 9 pounds (in 1 month), to 25 pounds (in 8 months). After the institution of therapy the weight curve was followed in 7 of the cases. All patients gained weight, and these varied from a minimum of 17 pounds (in 8 months) to a maximum of 40 pounds (in 6 months) (Table 2).

INCIDENCE. The oldest patient in the group was 35, the youngest 17, while the other 7 were between 25 and 31. This differs markedly from the usually accepted occurrence in patients "beyond the third decade," though in reports of large series it is found that the disease occurs before the fourth decade in from 3% to 15%[4,11,19,25,30] of the patients. At our hospital 11% of the cases are found in patients under 40, and about 5% under 35 years.[10] Isolated reports of pernicious

anemia in youth are not too infrequent[2,5,30] and it has even been reported in a 13-month old infant.[18] In spite of this we have been able to find only 1 case[34] in the literature which was similar to ours in detail and that was originally mis-diagnosed "sub-leukemic myelosis" by a very competent observer (the late Dr. R. H. Jaffee). That all our cases should have occurred in women was probably a coincidence, though it is conceivable that the added strain of pregnancies and menstruation will make a latent or mild pernicious anemia manifest itself earlier than it would otherwise.

The ratio of 5 negroes to 4 whites is out of all proportion to the incidence of the disease as seen at our hospital[10] where only approximately 8% of the patients with pernicious anemia are negroes. We do not know why there should be so striking a discrepancy. Neither the factors of diet nor blood loss varied sufficiently to explain the disproportion.

PHYSICAL FINDINGS. Fever was present in all our cases and in only 1 case was the peak below 100° F. Nothing, other than the anemia, was found to account for the fever in any 1 of the patients and in every case there was a subsidence of the fever after liver therapy was begun. Some elevation of the temperature is seen in almost every case of pernicious anemia in relapse, but the high fever as seen in these cases (Table 2 and Fig. 1) is relatively uncommon. According to Sherwood and Humphrey[29] Biermer was the first to comment on the occurrence of fever in pernicious anemia and much has been written on the subject since. In Cabot's series fever was a presenting complaint in only 3 of 1200 cases but was noted to be present in 475 of 691 cases. Fowler[8] found a temperature rise to from 102.4° F. to 106° F. in 8 of 206 cases at the time of the reticulocyte crisis. In these the fever subsided with the diminishing reticulocyte count and its height was unrelated to the original blood level.

Pallor and jaundice were prominent in almost every case and were usually noted by the patient as well as by the examiner. The degree of icterus varied considerably and was not demonstrably related to the severity of anemia.

Of the 6 cases in which note was made of the tongue, 4 were smooth, 1 was uncoated but not smooth, and 1 was *coated*. This represents an extraordinary finding since it is generally accepted that a coated tongue is very unusual in pernicious anemia.[33]

Systolic murmurs over the apex were heard in every case, presystolic murmurs in 3, diastolic murmurs in 2, and a mid-diastolic murmur in 1. Since the murmurs all disappeared following improvement in the blood it may be assumed that these were hemic murmurs and that no organic valvular changes were responsible.

Though the liver was palpable to from 1 to 8 cm. below the costal margin in 6 of the cases, only 1 patient showed tenderness over the liver area. Splenic enlargement of sufficient magnitude to make palpation possible was present in 7 cases and in 1 case the spleen extended to 8 cm. below the costal margin. Both the liver and spleen receded in size following the administration of liver therapy. This high incidence of splenomegaly differs from the usually found 20% as reported by

Cabot (290 of 1045 cases) and others,[3,33] and is much higher than that encountered by ourselves (5% to 10%).

Demonstrable edema was present in 5 cases. Occurring in about one-half the patients, this fits in well with the expected incidence and depends probably on the anemia and moderate heart failure for its appearance. Hypoprothrombinemia may be a contributing factor.

Only one patient showed significantly altered reflex changes. She had a positive Oppenheim's sign and positive ankle and patellar clonus. The others showed little neurologic changes excepting for occasional increase in deep reflexes. Vibration and position sensations were found intact whenever examined. This is unusual and bears emphasis since disturbed vibration sensation is a positive finding in about 90% to 95% of older patients with pernicious anemia.

RESPONSE TO THERAPY. The response to the intramuscular administration of liver extract was in every case favorable. There was, as is typical of pernicious anemia, a reticulocytosis which in every case approximated or even exceeded the mathematically expected "peak" in from 5 to 9 days.[9,12] The red cell and hemoglobin response were also quite characteristic.[26] But even more striking than the improvement of the blood was the improvement in the general condition.[33] These people—acutely ill on admission in many cases, weak, pale, feverish, and often unwell for many months—suddenly recovered their sense of well-being. Almost overnight their appetite returned, fever subsided and in a few days they were out of bed feeling better than they had for many months.

Transfusions, if adequate in quantity, wrought the same changes as liver but to a much less striking degree and for a much shorter time; and although they may have been of benefit in tiding the patients over the first few crucial days their lasting value was certainly slight.

Although both iron and dilute hydrochloric acid were used as adjuvants in the treatment of several of the cases, we feel that unless specifically indicated (i. e., for iron deficiency or gastro-intestinal symptoms of certain types) these drugs do not in any way alter the course of the disease.

BLOOD. Records of the blood findings before the initiation of therapy are available for 12 of the 14 admissions, each one representing a relapse in the course of the disease. For the most part the hematologic findings were typical and showed the characteristic anemia with the classical red cell changes, the leukopenia[28] with the granulocytopenia, the "right shift," and the multilobed macropolycytes[15] of the neutrophilic series, the occasional presence of nucleated red cells, and the characteristic reticulocyte response to liver therapy.[9,12,16]

The highest white cell count was 7150 while the lowest was 2300 per c.mm. The total white cells averaged 5100, with an absolute granulocytopenia in every case. The highest relative neutrophile count was 73% (of 5600 W.B.C.) and this occurred in a patient with a 2.94 million red count and severe bleeding.

In half the cases the number of reticulocytes reached or exceeded the mathematically expected maximal peaks,[12] while in the other half

the peaks fell below expectations. (Of interest is the fact that while the average expected maximal response was only 31%, the actual average was slightly over this, being 33%.)

The color index varied most significantly from the typical finding in pernicious anemia. In only 5 of the relapses was the color index significantly over 1.0, in 4 it was 1.0; and in 3 it was from 0.6 to 0.8 (Table 1). In all but 2 who had such low color indices there was a history of prolonged blood loss, either nasal or vaginal or both, and none of those who had such bleeding showed a color index of over 1.0. Of further interest is the fact that the 2, who in their first relapse showed low color indices, when later readmitted, no longer showed this, having in the interval received supplemental iron therapy.

Although an occasional case of pernicious anemia is seen with a low color index these cases are admittedly rare. When one considers the achlorhydria and the bizarre dietary history of many patients with pernicious anemia, it is surprising that frank iron deficiency is so rare. This is at times more apparent than real and iron deficiency frequently develops during the improvement of the blood following a remission induced by liver. It is not infrequent to find it necessary to supplement the liver therapy with iron when the red cell count reaches 3½ to 4 million and the hemoglobin remains at 60% to 70% (Fig. 2). Of course we deal here with a group differing in one very significant particular from the usual. These patients were all young women in the child-bearing, menstruating period of life and were subject to this added strain on their iron depots. There is little question that our concept of the blood in pernicious anemia would need revising if more of our patients fell into this age group.

Summary and Conclusions. Nine cases diagnosed by us as atypical pernicious anemia occurring in 4 white and 5 colored women, all under 35 years of age, are reported.

The similarities and dissimilarities between "textbook" cases of pernicious anemia and the presented cases are discussed.

The atypical manifestations of the disease especially as regards the youth of the patients, the symptoms and the frequent occurrence of high fever are stressed. The striking similarity of most of the cases to subacute bacterial endocarditis is demonstrated.

The presence of atypical blood findings due to bleeding and the concomitant development of iron deficiency is pointed out.

The necessity of including pernicious anemia in the differential diagnosis of severe anemias regardless of the age of the patient is emphasized.

REFERENCES

1. ADDISON, T.:   On the Constitutional and Local Effects of Disease of the Suprarenal Capsules, London, Highley, 8, 43, 1855.
2. ANDERSON, K. W.:   Minnesota Med., 13, 297, 1930.
3. BIGG, E.:   Ann. Int. Med., 14, 277, 1940.
4. CABOT, R. C.:   Osler's Modern Medicine, 4, 612, 1908.
5. CHEVALLIER, P., and ELY, A.:   Le Sang, 10, 1010, 1936.
6. DAMESHEK, W., and VALENTINE, E. H.:   Arch. Path., 23, 159, 1937.
6a. DAMESHEK, W., and SCHWARTZ, S. O.:   Medicine, 19, 231, 1940.

7. Draper, G.: Human Constitution, Philadelphia, W. B. Saunders Company, 1924.

8. Fowler, W. M.: J. Lab. and Clin. Med., 22, 155, 1936.

9. Friedman, A., Isaacs, R., and Lufkin, A.: J. Lab. and Clin. Med., 24, 677, 1939.

10. Gore, M., and Schwartz, S. O.: (In press.)

11. Holbee, S. A.: Hospital Stidende, 76, 72, 1933.

12. Isaacs, R., and Friedman, A.: Am. J. Med. Sci., 196, 718, 1938.

13. Isaacs, R.: Blood Cell Morphology in Constitutional Types and Heredity, Medical Papers Dedicated to Henry A. Christian, p. 538.

14. Jones, E.: Am. J. Med. Sci., 195, 150, 1938.

15. Jones, O. P.: Arch. Int. Med., 60, 1002, 1937.

16. Jones, O. P.: Proc. Soc. Exper. Biol. and Med., 38, 222, 1938.

17. Kahn, J. R.: Am. J. Med. Sci., 194, 463, 1937.

18. Langmead, F. S., and Doniach, I.: Lancet, 1, 1048, 1937.

19. Lindstrom, E.: Acta. med. Scand., 73, 71, 1930.

20. Mills, J., and Mawson, C. A.: Lancet, 2, 1455, 1938.

21. Minot, G. R., and Murphy, W. P.: J. Am. Med. Assn., 87, 470, 1926.

22. Moench, M. L.: Ann. Int. Med., 10, 1115, 1937.

23. Murphy, W. P., and Howard, I.: J. Am. Med. Assn., 112, 106, 1939.

24. Paddock, F. K., and Smith, K. E.: Am. J. Med. Sci., 198, 372, 1939.

25. Reed, E. B.: Nebraska State Med. J., 22, 312, 1937.

26. Riddle, M. C.: Am. J. Med. Sci., 200, 145, 1940.

27. Schindler, R., and Serby, A. M.: Arch. Int. Med., 63, 334, 1939.

28. Sharp, E. A., Schleicher, E. M., and Wolter, J. W.: Am. J. Clin. Path., 9, 189, 1939.

29. Sherwood, K. K., and Humphrey, W. R.: Minnesota Med., 13, 379, 1930.

30. Strandell, B.: Acta med. Scand., Suppl., vol. 40, 1931.

31. Strauss, M. B., and Pohle, F. J.: J. Am. Med. Assn., 114, 1318, 1940.

32. Stub, O.: Acta med. Scand., 81, 535, 1934.

33. Sturgis, C. C.: Bull. New York Acad. Med., 14, 715, 1938.

34. Van der Kloot, A.: Illinois Med. J., 71, 487, 1937.

35. Vatcher, S.: Lancet, 2, 192, 1939.

DYNAMICS OF AIR–BORNE INFECTION

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In the attempt to explain epidemics by the law of mass action the parasitic communication between host and victim has often been likened to the contact which is assumed to exist between reacting molecules.[1,2,4,7,8,9] Now, while contact is an elemental concept in chemical reaction, it describes, when used with reference to the epidemic spread of contagion, a complex ecologic phenomenon involving the behavior of a parasite and the response of a host (both conditioned by innate and acquired characteristics), and intricate modes of transmission between and within human aggregations. Moreover, the existence of an infection and its spread among human aggregations is not always clinically apparent, a fact which impedes the study of epidemic contagion. Nevertheless, it is possible to study the dynamics of contagion experimentally where simple examples of pure parasitism[3] are chosen.

In measles, for instance, infection produces a clinical picture. Persons are not naturally resistant to infection, but from it they do acquire lasting immunity. It is therefore possible to determine readily the number of persons within a group at a given time who are susceptible to this disease. The infection goes through a characteristic incubation period in human beings. This enables us to determine from the date on which the disease becomes clinically visible the approximate date at which effective exposure occurred, and to observe the chain of infections, thus locating the aggregation within which exposure occurred. Clustering of cases within a particular aggregation may further indicate the degree of exposure to a common infected air supply.

Under favorable conditions, statistical expression may be given to the probability of contact in air-borne infection. Statically, this will depend upon the presence in a given atmosphere at a given time of a certain concentration of infective material and a certain concentration of susceptible persons. The concentration of infective material varies according to the rate at which infective organisms are projected into or removed from the atmosphere.

Other factors remaining uniform, the rate at which infective material is contributed to the atmosphere by infected persons who have reached but not yet passed the infective stage depends largely upon the duration of this stage of the disease and the number of susceptibles infected during this time interval. If an epidemic is primarily air-borne, this means that the rate at which the air becomes infected depends also upon the rate at which susceptibles become infected by the air. The latter, however, depends upon the rate of the removal of infective material from the atmosphere by ventilation. Therefore, the volume of air change in the particular atmosphere per susceptible per minute, for purposes of convenience called "atmospheric density of susceptibles," is an important determinant of the rate of spread of air-borne infection.

The hypothesis is made, then, that in air-borne infection the atmospheric density of susceptibles may be reduced below a "threshold density,"[2] either by increasing ventilation or by reducing the number of susceptibles, and the aggregation may thus be rendered safe from epidemic spread of air-borne contagion. According to this hypothesis, threshold density of susceptibles varies with ventilation. The number of susceptibles sharing a given air supply at threshold density defines threshold ventilation, and increased ventilation would provide a proportionately larger number of susceptibles with threshold ventilation. Further, it has been demonstrated that irradiation of the atmosphere by ultraviolet light is equivalent to an increase in ventilation.

Now to study the dynamics of an epidemic of measles, we turn to the school, for, in a small community, childhood contagion is focussed in the school; also, from school records we can determine which children are susceptible to and which are immune from infection. If classroom aggregations of roughly similar numbers in a school population

are exposed for equal periods under similar conditions of ventilation, the atmospheric density of susceptibles varies in proportion to the percentage of susceptibles in each aggregation. If we describe contagion-spread in terms of percentage susceptibility curves (Chart 1), then the point of inflection marks a threshold density of susceptibles, at which spread is endemic, below which cases are sporadic, and above which epidemicity increases.

MEASLES
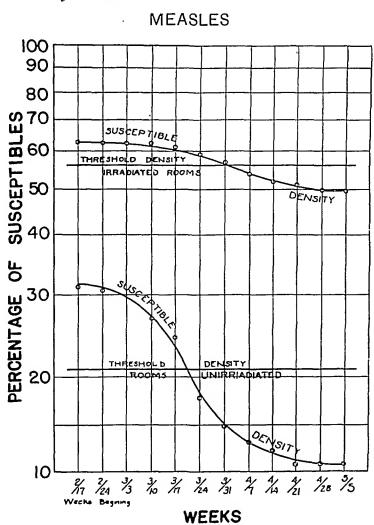
CHART 1.—Measles susceptibility in Germantown Friends School and Swarthmore Public Schools during 1941 epidemic (primary classrooms irradiated). Threshold density of susceptibles indicated at point of inflection in accordance with McKendrick's theory.

The point of inflection of the curve of proportionate decline in percentage of susceptible pupils in the unirradiated High School shown in Chart 1, theoretically indicates protection against epidemic spread of contagion by fivefold increase in equivalent ventilation. After the epidemic had spent itself, the percentage of susceptible children in the irradiated primary schools was higher than in the High School before it commenced; but the threshold in the irradiated primary schools indicates equivalent ventilation only 3 times greater. However, the fact that the inflection point was reached 13 days later (incubation period of measles) in the primary than in the High School indicates spread

from the latter rather than dynamic spread within primary school classrooms. The time-distribution of cases within the classes[6] also indicates that tenfold increase in equivalent ventilation, independently determined by bacteriologic methods of measuring sanitary ventilation,[5] prevented epidemic spread of measles in irradiated classrooms during the winter.

There are special reasons why the dynamic pattern of spread of measles during the record breaking epidemic of 1940–41 is so simple. Apart from the facts that measles is the natural prototype of an airborne contagion and that the schools provide an exceptional setting for a free performance, it was also true that onset was so swift, and infection so heavy, that the density of susceptibles was reduced below the community threshold before secondary spread outside the school could become established.

MUMPS
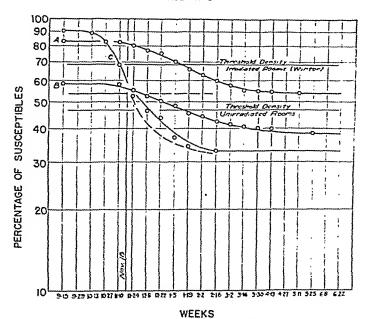
CHART 2.—Mumps susceptibility among school children of Swarthmore during 1941–42 epidemic. Curve C, showing epidemic spread in first 3 grades of College Avenue School, chiefly exposed on or before November 18. Curve A, showing endemic community spread in absence of epidemic classroom spread in Rutgers Avenue School and upper 3 grades of College Avenue School, chiefly exposed after November 18. Curve B, High School (unirradiated).

The dynamic pattern of spread of an epidemic of mumps through the community of Swarthmore during the succeeding year illustrates some of the factors, more particularly the interacting exposure between school and community, which complicate the experimental study of air-borne infection among human aggregations. A case of mumps, exposing the third grade of the College Avenue School on September 29 and 30, detonated an explosive accumulation of susceptible material. On the second and third generations, synchronous epidemic waves were initiated in the first and second grades, respectively. Epidemic waves of decreasing amplitude then fanned out on an ever-

widening front through the entire population of Swarthmore during the remainder of the season.

The change from epidemic to endemic spread of infection (Chart 2) probably represents a difference in atmospheric density of susceptibles. Epidemic spread, therefore, illustrated by curve C, probably indicates wide difference between threshold and initial sanitary ventilation per susceptible, while curves A and B approach endemic spread at threshold density. With similar initial susceptibility (curves A and C) sanitary ventilation differs; with equivalent ventilation (curves B and C) the difference in sanitary ventilation per susceptible could only be due to the higher initial number of susceptibles.

Difference between the autumn threshold of 3 irradiated primary classrooms first attacked (curve C), and winter threshold in the High School (curve B), could also be explained by various differences in the two schools.* Higher winter threshold densities in primary schools (curve A), however, under otherwise similar conditions, would be difficult to explain except for radiant disinfection. Winter differences in threshold, favoring irradiated primary schools over the unirradiated High School both for mumps and measles, also indicate control of epidemic spread of contagion in primary schools by tenfold increase in sanitary ventilation.

The curves A and C contrast epidemic classroom spread (curve C) with endemic community spread (curve A). In 3 of the primary classes first attacked, 32 out of 42 cases could have resulted from 23 classroom exposures, but only 15 of 73 cases in 11 remaining primary grades of comparable susceptibility could have resulted from 30 class exposures. Similarly, 31 of 51 cases in the two primary schools (Chart 3) could have been infected by 18 class exposures between September 30 and November 19, yet 53 class exposures between November 18 and April 7 could account for no more than 16 of the 64 cases infected after November 18, and some of these probably were extra-class infections. Moreover the percentage of class secondaries in the more susceptible and more heavily exposed Rutgers Ave. School was less than half that in the College Ave. School exposed earlier in the season (Chart 3). Some factor favorable to epidemic spread of mumps during mild, moist, fall weather appeared to be under control during cold winter weather.

We cannot here discuss the nature of the factors which might explain epidemic spread of mumps in 3 College Avenue classrooms conspicuous in the early school season, but which declined within the classrooms of both schools during the winter. But it is pertinent to point out the rôle of epidemic classroom spread in heavily seeding a large reservoir of susceptible school children in the community. The endemic harvest of cases resulting from this epidemic sowing would seem to indicate that the density of susceptibles was close to the community threshold.

* The difference could be explained by window ventilation in mild weather or difference between the atmospheric density of primary school susceptibles in classrooms where three-fourths of infections could have occurred and High School susceptibles in the community including classrooms, where only half of the cases could occur, or to naturally resistant children who might disproportionately influence the less susceptible group, even though secondary attack rates in homes were equal.

The identification of class secondaries made it possible to distinguish the epidemic intra-class from the endemic extra-class patterns of spread of contagion among pupils of the two schools, in the fall and winter. Without such differentiation, extra-mural infection of school children masks intra-mural protection, which may explain the disappointing results obtained in attempting to reduce incidence of colds by school irradiation.[5] Only when a major fraction of exposure is prevented, is it feasible to demonstrate control. Radiant disinfection
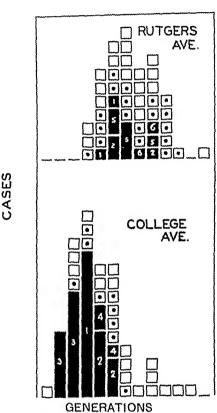
CHART 3.—Mumps in Swarthmore Primary Schools, 1941–42. Cases plotted against generation periods. First introduction September 30. Each bar represents one generation period beginning October 7, 25, November 10, 27, December 14, January 1, 19, February 6, 24, March 14, April 1, 19, May 9. Black bars indicate class secondaries defined by cases occurring from 13th to 22d day after class exposure on day of onset or previous day. White numbers on black bar represent the grade. White squares represent extra class infections. Black dots indicate home secondaries.

of the atmosphere of selected aggregations, nevertheless, offers an experimental technique for disclosing channels of epidemic spread of contagion within the community.

Summary. This paper presents the hypothesis that epidemic spread of contagion depends upon deficiency of air supplied per susceptible person. It presents data from our school studies which indicate that tenfold increase in winter ventilation or its equivalent by ultraviolet irradiation does control the epidemic spread of air-borne contagion.

REFERENCES

1. FROST, W. H.: Cutter Lectures, Harvard University, February, 1928. (Unpublished, cited by Zinsser and Wilson.)
2. MCKENDRICK, A. G.: Edinburgh Med. J., n.s. (ivth), 49, 117, 1940.
3. SMITH, THEOBALD: Parasitism and Disease, Princeton University Press, 1934.
4. SOPER, H. E.: J. Roy. Statist. Soc. London, 92, 34, 1929.
5. WELLS, W. F., WELLS, M. W., and WILDER, T.: Am. J. Hyg., 35, 97, 1942.
6. WELLS, W. F., and WELLS, M. W.: Am. J. Pub. Health, 28, 343, 1938.
7. WILSON, E. B., and BURKE, M. H.: Proc. Natl. Acad. Sci., 28, 361, 1942.
8. WILSON, E. B., and BURKE, M. H.: Proc. Natl. Acad. Sci., 29, 43, 1943.
9. ZINSSER, H., and WILSON, E. B.: J. Prev. Med., 6, 497, 1932.

STUDIES ON BONE MARROW IN VITRO

I. THE CELLULAR PATTERN AND BEHAVIOR OF EXPLANTED BONE MARROW

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THE conditions of the bone marrow in the living organism, its distribution over the entire body and the multiplicity of influences which affect its activities, render the evaluation of the factors which determine its functions difficult. In order to overcome these difficulties it seemed worthwhile to establish conditions under which the bone marrow may be kept alive outside the body as an organ with its characteristic structure and function. The response of the surviving bone marrow to various influences, such as changes in the media or the adding of various substances, could then be observed and registered. Thus, direct experiments on the bone marrow would become possible.

The classical method of tissue culture does not fulfill this purpose. Numerous attempts to culture bone marrow have shown that the bone marrow in vitro soon loses its characteristic structure. The extensive outgrowth and proliferation of cells in the culture result in the disintegration of the organ as a structural entity. The object of this investigation, on the other hand, was not to obtain cultures of different cell elements of bone marrow, but to study the surviving bone marrow itself, and its constituents as a whole.

The technique employed in our experiments, therefore, aimed at conditions which would favor the preservation of organ structure and possibly limit cell outgrowth. For this purpose advantage was taken of the method initiated by Loeb,[8] which consists in freely suspending explanted tissue fragments in tubes filled with plasma. The culture hanging in the plasma clot is deprived of its chief growth support, the plasma layers adjacent to the walls of the container, and therefore cell outwandering is definitely limited.

A similar method of explantation was employed by Jeney[5] in his study of the influence of various substances on the function of the bone marrow *in vitro*.*

Material and Methods. *Material.* Bone marrow was obtained from the tibia of 6–8 weeks old rabbits. The bone marrow of animals of this age is rich in parenchyma as compared with adult bone marrow. According to Sabin,[11] the erythroid hyperplasia of the rabbit's bone marrow, present since birth, has at this age been reduced; and the production of leukocytes has set in, in a measure corresponding to the demands of the peripheral blood. Our observations have shown, however, that even at this age the cellular composition of the bone marrow is not definitely fixed. There are marrows with predominant myeloid cells and others with predominant erythroid elements. Also the proportion of the mature to the immature cells varies considerably. The cell pattern type of the original bone marrow must be carefully noted, as it determines the course of development taking place in the explant *in vitro.*

Method of Explantation. The containers used for explantation were glass tubes of 1.5 cm. height and 8 mm. diameter. The bone marrow fragment of the size of 3 mm.³ was placed immediately after removal from the tibia in the medium, consisting of 3 drops of rabbit's plasma, 3 drops of Tyrode solution and 1 drop of diluted chick embryo extract. The tissue fragments were planted at the time when the plasma began to coagulate, so that it remained suspended in the upper layers of the medium. The tubes tightly closed were incubated at 37° C. After incubation the plasma clot containing the bone marrow explant was taken out and fixed. The plasma was obtained from the carotid of adult rabbits. To prevent coagulation, 5 drops of heparin were added to each 10 cc. of blood. The bone marrow explants were incubated for 24, 48, 72, 96 and 120 hours respectively.

Experiments (26) were carried out with bone marrow of 26 different rabbits. The bone marrow of 12 animals showed prevailing leukopoiesis; of 8, prevailing erythropoiesis; and in the bone marrow of 6 animals myeloid and erythroid cells were present in nearly equal proportions.

Histologic Technique. The material was fixed in Zenker's and Helly's fluid. After embedding the specimens in celloidin-paraffin, serial sections 4μ thick were made and stained with hematoxylin-eosin; frequently sections were also stained with Giemsa.

Differential Cell Counts on Bone Marrow Sections. The differential counts were made on 4μ thick sections. The counting was performed by using a small ocular diaphragm, and, because of the non-homogeneous distribution of the cells, different areas of the section were counted. In the sections of the original bone marrow 500 to 600 cells were counted. In the sections obtained from the explanted bone marrow fragments, all the cells present in one section were counted, including the surrounding plasma clot. The number of cells ranged between 500 and 800. The following cell types were differentiated: (1) stem cells; (2) promyelocytes and myelocytes; (3) metamyelocytes and polymorphonuclear leukocytes.

The value of such counts and the possibility of deriving from them reliable information about the changes taking place in the bone marrow, is a matter of discussion.[3,6,7,11,12,14]

* The method of Osgood,[9] on the other hand, differs from ours in that this author performs his experiments on surviving isolated cell elements of the bone marrow and not on the surviving bone marrow as a whole.

No differential counts of erythroid cells were made, since we were concerned in the first place with the relative proportions of mature and immature cells, and the counting of mature erythrocytes in bone marrow sections is impracticable.

Results. The bone marrow explant *after 24 hours* of incubation shows the network of stroma, myeloid parenchyma and fat cells well preserved and without signs of degeneration. The adjacent plasma contains a varying number of widely dispersed cells which have migrated from the explant.
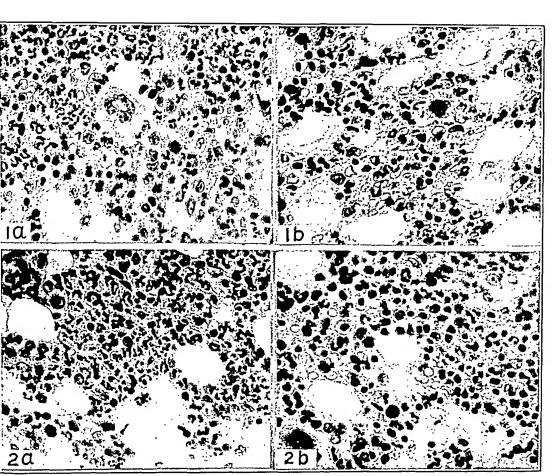
Fig. 1.—*a*, Explant of bone marrow (predominantly leukopoietic) after 24 hours of incubation. Hematox.-eos.; × 550. *b*, Corresponding original bone marrow. Hematox.-eos.; × 550.

Fig. 2.—*a*, Explant of bone marrow (predominantly leukopoietic) after 24 hours of incubation. Hematox.-eos.; × 550. *b*, Corresponding original bone marrow. Hematox.-eos.; × 550.

The changes which have taken place in the bone marrow during this period of incubation concern the *distribution* of the various marrow cells within the fragment and *a shift in the proportion* of the immature to the mature cells in favor of the latter.

Whereas in the original bone marrow the various cells or cell groups are more or less evenly distributed over the entire organ, the cell distribution in the 24-hour old explant is quite different. The central

parts of the fragment contain most of the mature granulocytes and their immediate precursors. They densely fill the trabeculæ and are often aggregated in large groups. Between them only relatively few immature cells are present (Figs. 1 and 2). As one approaches the periphery, the number of mature leukocytes progressively decreases and the number of immature cells increases respectively. The surrounding plasma again contains numerous segmented leukocytes, emigrated from the explant.

TABLE 1.—DIFFERENTIAL CELL COUNTS WITH PREDOMINANT LEUKOPOIETIC ACTIVITY

Animal No.		No. of cells counted	Stem cells (%)	Myelocytes (%)	Polymorpho-nuclear leukocytes (%)	Immature-mature ratio
R.19	A . . .	500	58,5		41,5	1:0,7
	B . . .	530	18,7		81,3	1:4,3
R.21	A . . .	600	2,2	41,2	56,6	1:1,3
	B . . .	660	1,4	26,6	70,0	1:2,5
R.24	A . . .	520	3,5	50,0	46,5	1:0,9
	B . . .	570	3,5	24,4	72,1	1:2,6
R.26	A . . .	500	4,8	51,0	44,2	1:0,8
	B . . .	600	6,1	22,2	71,7	1:2,5
R.27	A . . .	548	43,0		57,0	1:1,3
	B . . .	793	32,7		67,3	1:2,1
R.28	A	500	3,4	40,0	56,2	1:1,3
	B . .	500	2,8	22,8	74,4	1:2,9
R.29	A . . .	500	7,2	31,6	61,2	1:1,6
	B . . .	500	5,4	26,8	67,8	1:2,1
Av.	A . . .	524	4,1	42,8—	51,9—	
Av.	B . . .	597	3,8	24,6—	72,1—	

A = control section; B = section of 24-hour old explants.

The predominance of mature leukocytes over immature cells in the 24-hour old explants as compared with the original bone marrow is striking; this observation that maturation of leukocytes takes place *in vitro* could be substantiated by differential cell counts made on the myeloid cells of the original bone marrow sections and the sections of the explanted fragments respectively (Table 1). The table, which comprises differential cell counts of 7 of 12 experiments on bone marrow with predominant leukopoietic activity, reveals that the proportion of mature white cells to immature increases after 24 hours of incubation, the average increase being almost threefold.

Although the proportion of immature cells was found to be reduced after 24 hours of incubation, multiplication of the precursors doubtless takes place at a reduced rate, as evidenced by the considerable number of mitoses found in primitive blood cells. Occasional mitoses are also present in stroma cells. As a rule the number of mitoses in explanted bone marrow is even higher than that in the original material.

Table 2 gives the comparative number of mitoses in the original bone marrow and in the 24-hour old explants. It shows that the average number of mitoses in 10 fields (in each experiment 10 to 30

fields were counted) of the original bone marrow is 2.4; while the number of mitoses in an equal area of the explant is 9.0.

TABLE 2.—COMPARATIVE NUMBER OF MITOSES IN ORIGINAL BONE MARROW AND IN THE 24 HOUR OLD EXPLANTS

Animal No.		No. of mitoses in 10 fields	Animal No.		No. of mitoses in 10 fields
R.24	A	1	R.30	A	4
	B	7		B	12
R.27	A	4	R.35	A	1
	B	4		B	7
R.28	A	3	R.37	A	4
	B	9		B	5
R.29	A	2	R.41	A	0
	B	17		B	7

Av. A, 2.5; Av. B, 8.6.
A = control section; B = section of 24 hour old explants.

Mature erythrocytes also appear in increased numbers in explants of 24 hours as compared with the original bone marrow. Sinusoids filled with well-preserved erythrocytes mixed with a varying number of normoblasts could be regularly observed. The red cells often form large lakes filling in the meshes of the stroma (Figs. 3 and 4). Numerous erythroblasts are diffusely distributed over the entire marrow and are often in a state of mitosis. No red cells could be seen in the plasma, but they often concentrate at the borderline between the plasma and the explant.

Megakaryocytes are to be found scattered throughout the network of the stroma.

According to the prevalence of myeloid or erythroid cells respectively in the original material, the appearance of the explant after 24 hours varies. It is only in leukopoietic bone marrow that the maturation of leukocytes becomes clearly manifest. In bone marrow of a decidedly erythropoietic character the leukopoietic activity is slight, while the activity of the red series is marked.

After 48 hours of incubation, a somewhat different picture of the bone marrow explant is obtained. The center of the fragment contains many fewer marrow cells than after 24 hours. Here only a small number of leukocytes and their precursors are present. Most of the elements of the blood-forming parenchyma are to be found in the margin of the fragment. Here, a dense wall is formed mainly of immature cells, mixed with segmented leukocytes in varying proportions. All mature and immature blood cells as well as stroma cells and megakaryocytes are well preserved.

The red cells are numerous, especially in the bone marrow explants derived from an original marrow with predominantly erythropoietic activity. They are accumulated in large numbers, filling in the dilated sinusoids. Occasionally, red cells in large numbers are found also in the periphery of the sections. Because of the reduced number of leukocytes in the central parts of the sections after 48 hours of incubation, the red cells—mature erythrocytes mingled with few normoblasts and single erythroblasts—appear especially prominent.

Promyelocytes, myelocytes, and erythroblasts in mitosis are frequent, especially in the outer layers of the fragments.

The outstanding feature of the 48-hour old explant is, thus, the decrease in number of leukocytes in the center of the fragment, as compared with the 24-hour old explant; they are confined to the periphery of the fragment and to the adjacent plasma. The tendency of the polymorphonuclear leukocytes to migrate from the center, where they mature, to the periphery of the fragment and farther into the plasma, fully explains this picture.
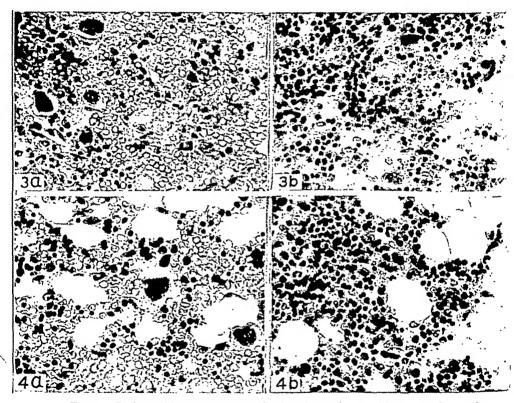
FIG. 3.—Explant of bone marrow (predominantly erythropoietic) after 24 hours of incubation. Hematox.-eos.; × 550. b, Corresponding original bone marrow. Hematox.-eos.; × 550.

FIG. 4.—a, Explant of bone marrow (predominantly erythropoietic) after 24 hours of incubation. Hematox.-eos.; × 550. b, Corresponding original bone marrow. Hematox.-eos.; × 550.

After 72 hours of incubation, the explant appears rather empty of cells, particularly in the central parts where only few myeloid and erythroid cells and megakaryocytes are to be seen. Also the massing of marrow cells at the periphery of the explant, seen in the 48-hour old explant, is far less pronounced. At this time a proliferation of stroma cells begins. In the periphery of the explant single and groups of spindle cells separate themselves from the stroma meshes and grow outwards

into the plasma. The primitive blood cells, that are found singly or in small groups between the stroma cells, are well preserved and show occasional mitoses. They may be situated also between the out-growing fibrocytes, always in a small number.

Both erythrocytes and normoblasts are still numerous in this stage. Megakaryocytes are well preserved.

The original organ structure of the bone marrow is hardly preserved in the explant examined *after 96 to 120 hours* of incubation. The pro-liferation of stroma cells, turning into fibrocytes, which has begun after 72 hours, has markedly progressed, not only in the periphery, but also in the central parts of the explants. The network of the stroma is collapsed and partly replaced by proliferating spindle cells. Among them myeloid elements in various stages of maturation are still present, and their multiplication is evidenced by the presence of mitoses, but their number is small. Even after 120 hours of incubation polymorpho-nuclear leukocytes, single or in groups, are to be found in the explant itself and also in the plasma clot. The erythrocytes are often still well preserved. Megakaryocytes occasionally show signs of degeneration, the nuclei having become pycnotic.

Comment. The experiments on explanted bone marrow have shown that bone marrow placed in a plasma medium *in vitro* gradually loses its organ structure. In the course of time the myeloid cells migrate from the explant and the stroma cells turn into fibrocytes. After 4 to 5 days the bone marrow *in vitro* is thus transformed into a culture of common spindle cells, interspersed with a few specific bone marrow cells, whose number continues to decrease. The process, however, which takes place during this period, is not one of depletion of paren-chyma and dedifferentiation only. Before these occur the blood ele-ments of the bone marrow undergo multiform changes, the description and interpretation of which form the content of this report.

The explanted bone marrow continues its activity *in vitro* at an even higher rate for a period, and it is only after this phase of activa-tion that regression sets in.

The functional activity of the bone marrow *in vitro* is manifested by two essential phenomena, cell maturation and cell multiplication.

Cell maturation involves equally the blood elements of both the red and white varieties. On inspection of the 24-hour old explant, one is impressed by the increased number of segmented leukocytes as well as of red cells, as compared with the control piece. Mature leukocytes fill in the trabeculæ and are present in large numbers in the central zone of the sections. Mature red cells are found in large masses, some-times in the form of lakes, at times surrounded by endothelial cells. The extent and the density of these aggregates are far greater than can be observed in normal bone marrow.

As mentioned above, maturation of erythrocytes could be assumed only by inspecting the histologic sections of the explant; to count them would be misleading. The relative increase in number of leukocytes could, on the other hand, be substantiated by differential cell counts made on the myeloid cells of the original bone marrow sections and the explanted fragments.

The question if maturation of blood cells takes place *in vitro* has been discussed by a number of authors and is still undecided.

Foot,[1,2] the first to study systematically cultures of chicken bone marrow, believed that he had seen the transformation of lymphoid cells (x-cells, large mononuclear leukocytes) into myelocytes and further into polymorphonuclear leukocytes. The same lymphoid cells may, according to this author, also develop into histiocytes.

Rasmussen,[10] in his experiments on cultures of rabbits' bone marrow, based his assumption, that maturation of myeloid cells takes place, *in vitro* on the following observations: (1) the presence of mature leukocytes in cultures after longer periods of incubation, ·in spite of the short life span of these cells; and (2) the shift in the proportion of mature to immature cells in favor of the first. In the course of cultivation observation of extrusion of the nuclei of normoblasts in bone marrow culture led this author to the conclusion that normoblasts mature *in vitro* into erythrocytes.

Van Herwerden,[4] too, was able to observe the maturation of normoblasts *in vitro* by extrusion of their nuclei.

Spadafina,[13] experimenting on cultures of rabbits' and guinea pigs' bone marrow, thought it probable that hemocytoblasts may develop into myelocytes and that normoblasts lose their nuclei and become erythrocytes, but Rasmussen states that no differentiation of the precursors of the normoblasts can be observed.

Under the conditions of our experiments we were able to establish with certainty the maturation of white blood cells in vitro; *and to regard as highly probable the maturation of red blood cells.*

Not only maturation but also multiplication of blood cells takes place in the bone marrow explants *in vitro*. Precursors of erythrocytes and leukocytes could often be seen in a state of mitotic division. Moreover, the number of mitoses in stem cells, myelocytes, and erythroblasts is always higher in the explanted than in the original bone marrow. The mitotic activity of the blood cells *in vitro* remains as long as immature cells are present, even after 5 days of incubation.

The histologic picture of the functioning bone marrow *in vitro* is very characteristic and differs in many features from that *in vivo*. Despite the fact that both aspects of bone marrow activity, multiplication and maturation, take place simultaneously in bone marrow explants *in vitro* in the same way as *in vivo*, the regulation of the cellular composition of the bone marrow *in vitro* is different and incomplete. Mature blood cells enter the blood stream in the living organism; they remain, however, within the culture, if explanted. Here they distribute themselves in the explant according to their locomotor capacities. The great motility of the leukocytes causes them to migrate from their place of origin to the periphery of the fragment and eventually into the free plasma. The mature red cells stay behind in the fragment. In this way the different cell types are sorted out zonally. Furthermore, bone marrow *in vivo* exhibits multiplication and maturation equally throughout its extent. *In vitro*, on the other hand, presumably on account of environmental factors, maturation of leukocytes takes place

predominantly in the central region of the marrow fragment, while multiplication is manifested more at the periphery. This is why in the beginning of incubation the center contains mainly mature cells, and the periphery mainly immature cells.

In normal bone marrow multiplication just balances maturation, and the release of mature white and red cells into the blood stream occurs at a certain pace, so that the relative proportions of the cell types present in the marrow remain practically the same. *In vitro* the multiplication of the primitive blood cells does not keep pace with maturation and migration, and mature cells are only partly replaced. Thus the number of specific bone marrow elements is reduced from day to day and the bone marrow becomes depleted.

No doubt can exist that this depletion is not brought about by a total *loss* of mitotic capacity on the part of the myelocytes and stem cells. As stated above, this capacity persists as long as primitive blood cells are present. It may be that this multiplication is insufficient in quantity, but it should be considered that the depletion of the bone marrow may also be due to a deficiency in the supply of specific blood cell elements by the altered stroma matrix. The bone marrow stroma is the first to lose its specific properties. At the time when myelocytes and stem cells are still present in a state of integrity, the reticular elements of the bone marrow begin to appear as fibroblasts. After 72 hours of incubation, when the cell content of the bone marrow fragment definitely decreases, the proliferation of fibroblasts sets in. This process of bone marrow depletion and fibroblast proliferation results finally in almost complete disintegration of the bone marrow as a specific functioning tissue, which becomes replaced by common mesenchyme cells.

As stated in our introduction, the object of this investigation was to establish a physiologic model which would help in the analysis of the factors which govern normal and pathologic blood cell formation in the bone marrow. The above-described method of bone marrow explantation, and the observations made on the explanted bone marrow, give reason to assume that this may be possible.

The bone marrow *in vitro* continues for a certain period of time the specific functional activity, even at an increased rate. This period of functional activity of bone marrow *in vitro* can be made use of in the study of the factors which affect the bone marrow function.

These studies are to be the subject of subsequent reports.

Summary. 1. A method is described which enables bone marrow fragments to survive *in vitro* for a certain period of time with preservation of its specific organ properties.

2. Maturation and multiplication of white and red cells was observed to take place in explanted bone marrow; maturation of polymorphonuclear leukocytes *in vitro* was proved by differential cell counts.

3. The period of functional activity of the explanted bone marrow is followed by depletion of the marrow parenchyma and fibroblastic proliferation of the stroma.

REFERENCES

1. Foot, N. C.: Beitr. z. path. Anat. u. z. allg. Path., 53, 446, 1912.
2. Foot, N. C.: J. Exper. Med., 17, 43, 1913.
3. Gall, E. A.: Am. J. Path,. 13, 575, 1937.
4. Herwerden, van M.: Arch. néerl. physiol., 8, 592, 1923.
5. Jeney, A.: Virchow's Arch. f. path. Anat., 287, 373, 1932.
6. Kindred, I. E.: Am. J. Anat., 67, 99, 1940.
7. Krumbhaar, E. B., and Custer, R. P.: Am. J. Med. Sci., 189, 630, 1935.
8. Loeb, L., and Fleischer, M. S.: Biochem. Ztschr., 36, 98, 1911.
9. Osgood, E. E., and Brownlee, I. E.: J. Am. Med. Assn., 107, 123, 1936.
10. Rasmussen, H.: Arch. f. exper. Zellforsch., 14, 285, 1933.
11. Sabin, F. R., Miller, F. R., Smithburn, K. C., Thomas, R. M., and Hummel, L. E.: J. Exper. Med., 64, 97, 1936.
12. Sabin, F. R.: Physiol. Rev., 8, 219, 1928.
13. Spadafina, L.: Arch. f. exper. Zellforsch., 17, 43, 1935.
14. Stasney, I., and Higgins, G. M.: Am. J. Med. Sci., 193, 462, 1937.

TISSUE CULTURE STUDIES ON CYTOTOXICITY OF BACTERICIDAL AGENTS

II. Effect of Tyrothricin, Gramicidin and Tyrocidine on Culture of Mammalian Spleen

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It has been observed that gramicidin is more toxic than tyrocidine for small wandering cells migrating from explants of mesenteric lymph node of the rabbit.[1]   The largest amount of tyrocidine which could be used in this type of preparation did not cause a significant degree of inhibition.   In order to compare the relative cytotoxic effect of tyrothricin and its fractions, gramicidin and tyrocidine, experiments were done in which tissues were grown in a plasma clot in Carrel flasks for a period of 4 days.   Rabbit spleen was used as a source of tissue because it is fairly homogeneous and provides a good source of large wandering cells or macrophages.

Experimental Studies.   Plasma and tissue extract were prepared in a manner previously described.[1]   Young, adult, male rabbits were used exclusively and the plasma, serum and tissues used in each experiment were obtained from the same animal.   A serum-chick-embryo extract was made by extracting chick embryos of 8 days of incubation with rabbit's serum in the proportion of one embryo to 5 cc. of serum.   The spleen was removed from the rabbit aseptically as soon after death as possible.   Fat and mesentery were removed from the spleen which was fragmented without any attempt to remove the capsule.   Fragments of a suitable size, approximately 1 to 2 mm. across, were placed in Tyrode's solution in three matched groups of 12 fragments each. One group of 12 fragments was used in cultures of the control series and the other two groups comprised the test series.   To one of the test series was added

one of the products of *B. brevis* and to the second test series was added an equal amount of another fraction of the soil bacillus. Thus, the effect of similar amounts of two fractions could be compared at one time.

In addition, a group of experiments was done in order to find the amount of variation in extent of growth exhibited by the various cell types originating from the splenic fragments. Each experiment in this group consisted of three normal series of 12 fragments each. No bactericidal agent was added to cultures in this group of experiments.

The bactericidal agents used in the test series were added to the tissue extract before the cultures were made. The crude tyrothricin and purified tyrocidine hydrochloride used in this study were obtained through the courtesy of Sharp & Dohme. Purified gramicidin was prepared by Osterberg according to the method of Hotchkiss and Dubos. Stock solutions were prepared containing 2% of the bactericidal substances in 95% alcohol. At the time of culturing, dilutions of the stock solution were made in Tyrode's solution. The resulting suspensions were added to the serum-chick-embryo extract in an amount that comprised one-twentieth of the total volume of the media used in making the preparation. The pH of the medium as determined by the glass electrode was not altered by the amounts of bactericidal substances used. Suitable dilutions of 95% alcohol in Tyrode's solution were added in a similar manner to the control series.

Cultures were planted in D5 Carrel flasks. Each preparation consisted of 0.5 cc. of heparinized plasma, 1 cc. of serum-chick-embryo extract containing the test substance and 4 explants of spleen placed in the resulting tissue culture clot. Three flasks, each of which contained 4 fragments, or a total of 12 fragments, were used for each experimental condition. All of the cultures comprising a single experiment were completed in as short a time as possible. The flasks were corked and sealed with a mixture of paraffin and petrolatum.

When clotting was complete, a camera lucida drawing was made of the outer edge of each fragment at a magnification of ×7. The cultures were then incubated at 37.5° C. for 4 days. After 96 hours of incubation the cultures were removed from the incubator and measurements were made of the extent of migration of the large wandering cells. This was done with the use of an ocular micrometer at a magnification of ×60. A measurement was made of the radius of the widest part of the migration zone from the edge of the original fragment to the periphery of the migration zone. Measurements were determined to the nearest 10 unit mark on the ocular micrometer. The average value in micrometer units was determined for each series of 12 cultures. The areas of the tracings of the original fragments were measured with a planimeter and the values expressed in planimeter units.

Tissue Culture Observations. Microscopic examination of the living cultures to which no bactericidal agent was added revealed the following sequence of events. During the first 24 hours of incubation many small wandering cells appeared in the migration zone. These consisted of polymorphonuclear leukocytes, lymphocytes and a few monocytes. The resulting mixed cell picture varied somewhat in different animals and a quantitative estimation of the degree of migration at this time gave irregular results. There was some extension of migration of the small wandering cells on the 2d day; however, they began to degenerate rapidly after the 1st day of migration. On the 2d day large wandering cells began to appear near the fragment. These cells increased in number and size, engulfing cellular débris in the migration zone. By the 4th day the macrophages had migrated beyond the limits of migration of the leukocytes. At this time many of the macrophages had become granular in appearance and there was little further migration after the 4th day. On the 2d or 3d day of incubation

fibroblasts began to grow out from the explant, and by the 4th day there was usually a narrow zone of fibroblastic growth around each explant.

The addition of toxic amounts of the three products of the soil bacillus caused varying degrees of cellular degeneration which affected all cell types to a somewhat similar extent. No qualitative differences between the action of tyrothricin, gramicidin and tyrocidine were observed in the unstained specimens. Cultures showing definite inhibition of migration of macrophages also showed a visible increase in degeneration of these cells as well as of the granular leukocytes and lymphocytes. The reaction of the growth of fibroblasts in the presence of the products tested was very irregular and further growth of the fibroblasts after the 4th day resulted in the new growth pulling away from the clot in many instances. For this reason reliable quantitative determinations could not be made on the fibroblasts.

TABLE 1.—MEASUREMENTS RECORDED ON MIGRATION OF MACROPHAGES FROM EXPLANTS OF NORMAL RABBIT SPLEEN

Experiment 1 (Control Series)

	Series 1		Series 2		Series 3	
Flask	Fragment size, planimeter units	Radius of migration of macrophages, ocular micrometer units	Fragment size, planimeter units	Radius of migration of macrophages, ocular micrometer units	Fragment size, planimeter units	Radius of migration of macrophages, ocular micrometer units
1	0 854	690	0 606	710	0.605	770
1	0.587	650	0.721	760	0.684	760
1	0.733	820	0.608	750	0.679	760
1	0.643	680	0.690	700	0.745	840
2	0.644	750	0.421	540	0 584	680
2	0.532	780	0.556	740	0.670	790
2	0.662	670	0.751	640	0.701	800
2	0.449	740	0.515	710	0.560	650
3	0.469	640	0 716	790	0.772	790
3	0 650	840	0.586	640	0.658	610
3	0 665	780	0.547	740	0.482	750
3	0 778	730	0 758	750	0.548	690
Mean	. . .	731	. . .	706	. . .	741
Standard deviation	66		. . .	69	. . .	68

Quantitative Observations. A study was made of the group of experiments in which no drug was added to the cultures. This was done in order to find the degree of variation existing between the three normal series of cultures and also to determine some of the factors influencing the results. Data from a typical experiment are presented in detail in Table 1. It can be seen that there was no definite relation between the size of the individual fragment and the extent of migration of macrophages. This was found to be the case in other experiments in the normal group. There was considerable variability of the extent of migration about the fragments within each series; however, the means are in good agreement. Table 2 shows the extent of variability in 6 such experiments. For convenience, the extent of migration of the second and third series of cultures, respectively, has been compared with that of the first series just as in the experiments in which germi-

cides were employed. The variability determined in this way did not exceed 10%. There was a great deal of variation between experiments performed on different days, which necessitated a direct comparison of the cultures containing germicides with a normal control series in each experiment.

TABLE 2.—MIGRATION OF MACROPHAGES FROM EXPLANTS OF NORMAL RABBIT SPLEEN

Control Group

Experiment	Series 1	Series 2		Series 3	
	Radius of migration, mean*	Radius of migration, mean	% difference from Series 1	Radius of migration, mean	% difference from Series 1
1	731 ± 19	706 ± 20	−3.8	741 ± 20	+1.4
2	481 ± 20	477 ± 23	−0.8	497 ± 17	+3.3
3	492 ± 22	483 ± 24	−1.8	468 ± 25	−4 9
4	552 ± 37	566 ± 31	+2.5	559 ± 22	+1.3
5	759 ± 25	752 ± 43	−0.9	831 ± 25	+9 5
6	613 ± 38	649 ± 20	+5.9	643 ± 26	+4.9

* The value following the ± is the standard error of the mean.

TABLE 3.—EFFECT OF 10 μG. PER CC. OF GRAMICIDIN AND TYROTHRICIN ON MIGRATION OF MACROPHAGES FROM EXPLANT OF NORMAL RABBIT SPLEEN

Experiment	Series 1 Control	Series 2 10 μg. per cc. gramicidin		Series 3 10 μg. per cc. tyrothricin	
	Radius of migration, mean*	Radius of migration, mean	% difference from control	Radius of migration, mean	% difference from control
1	498 ± 34	315 ± 14	−36.7	352 ± 16	−29.3
2	495 ± 16	213 ± 6	−57.0	376 ± 18	−24 0
3	380 ± 18	125 ± 9	−67.1	272 ± 14	−28 4
4	557 ± 19	307 ± 11	−44.9	446 ± 21	−19 9
5	534 ± 14	288 ± 16	−46.1	408 ± 23	−23 6

* The value following the ± is the standard error of the mean.

TABLE 4.—EFFECT OF 20 μG PER CC. OF GRAMICIDIN AND TYROCIDINE ON MIGRATION OF MACROPHAGES FROM EXPLANT OF NORMAL RABBIT SPLEEN

Experiment	Series 1 Control	Series 2 20 μg. per cc. gramicidin		Series 3 20 μg. per cc. tyrocidine	
	Radius of migration, mean*	Radius of migration, mean	% difference from control	Radius of migration, mean	% difference from control
1	629 ± 16	377 ± 21	−40.1	634 ± 33	+0 8
2	621 ± 27	138 ± 18	−77.8	653 ± 31	+5 2
3	402 ± 39	285 ± 32	−42.1	506 ± 31	+2 8
4	516 ± 25	208 ± 10	−59 7	553 ± 17	+7 2
5	337 ± 16	126 ± 11	−62.6	317 ± 26	−5 9

* The value following the ± is the standard error of the mean.

TABLE 5.—EFFECT OF 100 μG. PER CC. TYROTHRICIN AND TYROCIDINE ON MIGRATION OF MACROPHAGES FROM EXPLANT OF NORMAL RABBIT SPLEEN

Experiment	Series 1 Control	Series 2 100 μg. per cc. tyrothricin		Series 3 100 μg. per cc. tyrocidine	
	Radius of migration, mean*	Radius of migration, mean	% difference from control	Radius of migration, mean	% difference from control
1	527 ± 21	117 ± 11	−77.8	433 ± 20	−17 8
2	793 ± 28	171 ± 10	−78.4	642 ± 18	−19 0
3	684 ± 17	252 ± 25	−63 2	468 ± 40	−31 6
4	516 ± 21	189 ± 10	−63 4	445 ± 19	−13 8
5	499 ± 30	152 ± 12	−69 5	475 ± 36	− 4 8

* The value following the ± is the standard error of the mean.

When 10 μg. per cc. of either gramicidin or tyrothricin was added to the test series of cultures, there resulted a definite decrease of migration of the macrophages. Gramicidin caused more inhibition than tyrothricin (Table 3). On the other hand, 20 μg. per cc. of tyrocidine did not inhibit migration (Table 4). A significant, but comparatively small degree of inhibition resulted from the use of 100 μg. per cc. of tyrocidine (Table 5). It is difficult to compare accurately the relative toxicity of these agents; however, the results obtained permit the conclusion that gramicidin is more toxic than either tyrothricin or tyrocidine. For example, 10 μg. per cc. of gramicidin caused a greater decrease of migration than 100 μg. per cc. of tyrocidine. Furthermore, tyrothricin is definitely more toxic than tyrocidine. In Table 6 appears a summary of the results obtained in the entire group of experiments included in this study.

TABLE 6.—SUMMARY—INHIBITORY EFFECT OF VARIOUS DILUTIONS OF DRUGS ON THE MIGRATION OF MACROPHAGES

Drug	Amount, μg. per cc.	Experiments	% inhibition on migration of macrophages
Control	..	6	− 4.9 to + 9.5
Gramicidin	10	5	−36.7 to −67.1
Gramicidin	20	5	−40.1 to −77.8
Tyrothricin	10	5	−19.9 to −29.3
Tyrothricin	100	5	−63.2 to −78.4
Tyrocidine	20	5	− 5.9 to + 7.2
Tyrocidine	100	5	− 4.8 to −31.6

Comment. Present methods of extraction indicate that tyrothricin consists of 10% to 20% of gramicidin and 40% to 60% of tyrocidine. The results of the present experiments would indicate that the toxicity of tyrothricin is slightly greater than one would expect from its theoretical content of gramicidin and tyrocidine. This may be due to the fact that not all of the gramicidin is removed by the present methods of separation. At any rate, it appears that most of the cytotoxicity of tyrothricin is accounted for by its content of gramicidin.

It should be emphasized again that the cytotoxicity of products of *B. brevis* is low compared with that of a number of other germicides. This agrees with the absence of deleterious effects on the tissues when aqueous suspensions of these substances are used in the local treatment of infections. The amount of gramicidin necessary to cause a decrease in migration of lymphocytes of 20% to 25% in 24 hours is 100 μg. per cc.[1] On the other hand, only 0.5 μg. per cc. of gramicidin will cause complete hemolysis of erythrocytes suspended in the tissue culture medium in the same time.[3] In spite of their low toxicity for tissues, the products of *B. brevis*, gramicidin in particular, are lethal in small amounts when injected into the blood stream.[4,5] In addition to the destruction of erythrocytes, there is also the possibility that other cell systems are subject to damage, particularly when relatively large amounts are given and the animal dies in a few hours. Some of the experiments reported by Robinson and Molitor indicate that this might be the case.[4] When smaller amounts are given over a longer period of time as in the experiments of MacLeod, Mirick and Curnen, destruction of erythrocytes appears to be an important factor.

Conclusions. When the toxicity of the products of *B. brevis* is determined by their ability to inhibit the migration of macrophages from the normal rabbit's spleen in a medium composed of serum, plasma and chick-embryo-extract, it appears that gramicidin is most toxic; tyrothricin is next in order of toxicity, and tyrocidine is much less toxic than either gramicidin or tyrothricin. The greater part of the cytotoxicity of tyrothricin is accounted for by its content of gramicidin.

REFERENCES

1. HERRELL, W. E., and HEILMAN, D.: Tissue Culture Studies on Cytotoxicity of Bactericidal Agents: I. Effect of Gramicidin, Tyrocidine and Penicillin on Cultures of Mammalian Lymph Node, AM. J. MED. SCI., 205, 157, 1943.
2. HERRELL, W. E., and HEILMAN, D.: J. Clin. Invest., 20, 583, 1941.
3. HOTCHKISS, R. D., and DUBOS, R. J.: J. Biol. Chem., 141, 155, 1941.
4. MACLEOD, C. M., MIRICK, G. S., and CURNEN, E. C.: Proc. Soc. Exp. Biol. and Med., 43, 461, 1940.
5. ROBINSON, H. J., and MOLITOR, H.: J. Pharm. and Exp. Ther., 74, 75, 1942.

THE CLINICAL SIGNIFICANCE OF LOUD AORTIC AND APICAL SYSTOLIC HEART MURMURS WITHOUT DIASTOLIC MURMURS*

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THE clinical significance of systolic heart murmurs continues to be a controversial subject ever since they were identified over 100 years ago. In the earlier years of the practice of auscultation, the subject of heart disease revolved almost entirely around the presence or absence of murmurs which were given paramount significance. At that time valve defects occupied a position analogous to that of etiology under our present system of diagnosis. Sir James Mackenzie realized the fallacy of such an extreme concept with regard to apical systolic murmurs and began a campaign to discourage the idea that systolic murmurs were of fundamental importance as evidence of heart disease. This campaign was carried on by his pupil, Sir Thomas Lewis. They were so successful in this work that the profession departed radically from the original view. Indeed it seems that for the most part physicians have come to regard systolic murmurs anywhere as of little significance. Mackenzie did not believe that systolic murmurs should be ignored, since he stated that the systolic murmur is one of the common physical findings in heart disease, but he did wish to emphasize that the systolic murmur is not usually an important finding.

So general an acceptance by the profession of the unimportance of

systolic murmurs made it necessary for those interested in heart disease to attempt a clarification of the issue. This task has been of even greater magnitude than that originally undertaken by Mackenzie, and is still far from completed. Our own interest in it has extended over a considerable number of years. In 1927 one of us (P. D. W.),[6] after a study of apical systolic murmurs, found that longevity was decreased in the presence of loud systolic murmurs, and concluded that the prognosis became increasingly grave with the increased intensity of the murmur. With added experience since then, the present follow-up study was undertaken to include aortic in addition to apical systolic murmurs in the absence of diastolic murmurs. The clinical importance of the latter is universally acknowledged.

Material. This report is the result of a follow-up study of private cases seen by us 10 or more years ago. We chose those cases who, when first seen, had a loud systolic murmur heard best at either the aortic or apical area, without a diastolic murmur being present. We undertook to determine the status of these patients after an elapsed period varying from 10 to 21 years.

For the present study we included only those cases in whom the murmur was recorded as being loud or very loud (Grades 4, 5 and 6 of Levine's classification of murmurs). The rigidity of the criteria is attested to by the fact that only 273 such murmurs were found in the records of 6413 cardiovascular cases. Systolic murmurs of slight or moderate intensity (Grades 1, 2, and 3 of Levine's classification) were omitted; we hope to follow up those at a future date.

With respect to location, it may be said that all of these murmurs were widely transmitted; however, they were included only when it was definitely stated that the maximum intensity was either at the aortic or apical area. We have found that loud systolic murmurs arising in the aortic valve area are often well heard at the cardiac apex but not well heard at the lung bases, while loud systolic murmurs arising at the mitral area are well heard at the lung bases but not at the aortic area. This is a helpful but little recognized criterion.

By interviewing the patients personally or by letter, or through the patients' physicians or relatives, we were able to get satisfactory up-to-date information concerning 187 of the original 273 patients. Follow-up data on the remaining 86 cases were either inadequate or missing. There were 72 females and 115 males. The average age of the group at the time of the first examination was 56 years; 49 were under the age of 50 when first seen by us.

The accumulated data were analyzed in several respects but we were particularly interested in prognosis.

Analysis Relative to Etiology, Sex, and Location of Murmurs. From the etiologic point of view we have divided the series into five groups. Those patients whose heart disease was caused by coronary arteriosclerosis, hypertension, or both, were placed in the so-called degenerative group. In Table 1 it is evident that the incidence of "degenerative" heart disease was much greater than that of any other type. One hundred and twenty-four (66.3%) of the 187 cases were placed

in this group.   As might be anticipated, the age of these patients was relatively advanced when first seen.   The average age of the group was 64 years; only 4 were under 50.

Forty patients (21.3%) of the series were placed in the rheumatic group.   The average age of these patients was 35 years when they were first seen.   Twenty-four (60%) of these gave a definite history of rheumatic fever.   This is quite comparable to the incidence of rheumatic history noted in stenotic mitral valve lesions in patients of this age group.

TABLE 1.—LOUD SYSTOLIC MURMURS WITH RESPECT TO ETIOLOGY, SEX AND LOCATION

Sex	Location	Degenerative	Rheumatic	Congenital	Luetic	Uncertain	Total
Male	Apical	73 } 85	11 } 16	0	0	10 } 12	94 } 115
	Aortic	12	5	1	1	2	21
Female	Apical	31 } 39	21 } 24	1	0	6 } 8	59 } 72
	Aortic	8	3	0	0	2	13
Total		124	40	2	1	20	187

In 20 patients (10.7%), the etiology of the heart disease was uncertain.   In several cases the uncertainty revolved about the question of rheumatic etiology.   In some, the presence of multiple etiologic factors was confusing and made classification impossible.   In a few cases no definite cause could be determined.   We believe that a considerable number of the cases in this group were rheumatic in type. The average age of the group at the first examination was 49 years.

In the remaining two groups there were 2 patients with congenital and 1 with luetic heart disease.

Of the total of 187 patients there were 115 (61.4%) males and 72 (38.6%) females.   The predominance of males was slightly higher among those with "degenerative" heart disease than in the group as a whole, 68.5% being of this sex.

In the group of uncertain etiology the incidence of males was 60%, while in the rheumatic group only 40% were males.

When the relative frequency of loud systolic murmurs with maximum intensity at the aortic and apical areas was considered, it was found that aortic murmurs were in the minority, only 18.1% of the total number being so located.   We found that systolic murmurs of this intensity at the aortic area unaccompanied by a diastolic murmur, were relatively uncommon.   Among the 34 patients who had aortic systolic murmurs, aortic stenosis was diagnosed 18 times and a questionable diagnosis of aortic stenosis was made twice.   In 3, the diagnosis was made after a considerable period of observation, the murmur being considered of maximum intensity at the apex on the first examination in 2 of these.   A diastolic aortic murmur was recorded terminally in 1 patient.

Etiology had no striking effect on the relative frequency of murmurs in the two locations.   Aortic systolic murmurs constituted 20% of the total number noted in both the rheumatic group and the group of uncertain etiology.   In the degenerative group aortic systolic murmurs were found in 16.1% of the patients.   Also the relative frequency was

not affected by sex since in 18.2% of the males the murmurs was of greatest intensity at the aortic area as compared with 18% of the females.

A Study of Mortality. The results of our follow-up study showed that of the total of 187 patients, 155 (82.8%) had died. The remaining 32 patients were living at the time of our last information, which was 10 or more years after their initial examination; however, since in some cases the last information was dated some time before these data were assembled some of these persons may have since succumbed.

The cause of death in the patients is both of interest and of importance. We were unable to learn the exact cause of death in 13 patients. However, facts indicate that in 7 of these death was probably due to cardiovascular disease; no surmise was justified in the remaining 6. Of the 142 patients in whom the cause of death was determined, 131 (92.2%) died of cardiovascular disease. In 122 (85.9%) death was directly cardiac in nature, subacute bacterial endocarditis accounting for 7 of these fatalities. There were 9 deaths due to cardiovascular disease, though not directly due to the heart. One exitus was caused by uremia, and in 8 a cerebrovascular accident was the terminal event.

Disease not related to the cardiovascular system was responsible for 11 deaths, though heart disease may have been of some secondary importance in a few of these. Postoperative deaths occurred in 3 of the 11 persons. Pneumonia was the cause of death in 3 others, while carcinoma of the stomach, perforated peptic ulcer, liver damage due to cinchophen, an automobile accident, and tetanus, each accounted for 1 death. In Table 2 the known non-cardiac deaths occurring in each etiologic group are indicated by figures in parenthesis.

The fact that 122 (65.2%) of these patients with loud systolic murmurs are known to have died cardiac deaths indicates the prevalence of serious heart disease among these persons.

TABLE 2.—LOUD SYSTOLIC MURMURS. MORTALITY AFTER 10 AND 15 YEAR
INTERVALS ACCORDING TO ETIOLOGY

			Etiology		
		Follow-up interval	Total cases followed	Living	Dead	Mortality (%)
Degenerative	. .	10 yrs.	124	19	105 (14)	84.6
		15 yrs.	119	2	117 (16)	98.3
Rheumatic	. . .	10 yrs.	40	21	19 (3)	47.5
		15 yrs.	33	8	25 (4)	75.7
Cause	. . . .	10 yrs.	20 .	10	10	50.0
		15 yrs.	15	3	12	80.0
Congenital	. . .	10 yrs.	2	1	1	50.0
		15 yrs.	1	0	1	100.0
Luetic	. . . .	10 yrs.	1	1	0	0.0
		15 yrs.	0	0	0	0.0
Total .	. . . .	10 yrs.	187	52	135	72.1
		15 yrs.	168	13	155	92.0

Numbers in parentheses indicate those who died of non-cardiac cause.

Status After 10 and 15 Year Intervals.   It was considered advisable to determine the exact status of these patients at the end of a definite follow-up interval.   Since the status of all 187 patients was known at the end of 10 years, this was taken as one follow-up period, and since by coincidence all known deaths occurred within 15 years following the initial examination, this was taken as a second follow-up period.   Of those patients who survived 10 years all trace was lost of 19 before 15 years had elapsed; therefore, only 168 patients were included in the 15 year follow-up.   In Table 2 the mortality of each etiologic group, as well as the total mortality for each of these periods, is indicated.

By the end of 10 years 135 (72.1%) of the 187 patients followed, had succumbed.   The mortality among those with degenerative heart disease was extremely high, 84.6% having died.   Though the death rate among those with heart disease of rheumatic and of uncertain etiology was less, it was still high, 47.5% of those with rheumatic heart disease and 50% of those with heart disease of uncertain etiology having died.

If those patients who were known to have died non-cardiac deaths are eliminated, we find that 73.5% of the degenerative, 40% of the rheumatic, and 50% of the group of uncertain etiology died within 10 years.

At the end of an elapsed period of 15 years 155 (92%) of the 168 patients followed were dead.   Nearly all (98.3%) of those with degenerative heart disease were dead.   Of those patients with rheumatic heart disease 75.7% were dead and 80% of those with heart disease of uncertain etiology had succumbed.   If non-cardiac deaths are eliminated, the mortality of the degenerative group is reduced to 84.8%, that of the rheumatic group to 60.6%, while that of the group of questionable etiology is unchanged.

Since there are included 13 deaths in which the cause was not ascertained it cannot be assumed that all deaths other than those designated as non-cardiac were due to heart disease.   While some of these may have died of other causes the number would not be sufficient to alter materially the mortality percentages given after the known non-cardiac deaths were deducted.

Though it is not known how many of those patients with rheumatic heart disease would have died cardiac deaths had not death from a non-cardiac cause intervened, it seems fair to conclude that loud systolic murmurs of rheumatic etiology have a somewhat better prognosis. We believe that there are several reasons for the marked difference in mortality between the degenerative and the rheumatic types of heart disease.   First, the course of degenerative heart disease is usually shorter than that of the rheumatic type.   The fact that the average age of those with rheumatic heart disease was nearly 30 years less than that of the degenerative group also had a marked influence on the death rate.   We believe that a more important reason, and one closely related to the presence of the murmur itself, is that loud systolic murmurs in the apical region in those with degenerative heart disease are due to relative mitral insufficiency, cardiac hypertrophy and dilatation

being both more frequent and more marked.   The serious impairment of cardiac reserve which this implies is reflected in the mortality of the group.

TABLE 3.—LOUD SYSTOLIC MURMURS. THE RELATION OF SEX AND LOCATION OF THE MURMUR TO MORTALITY

	Elapsed interval	Total	Alive	Dead	Mortality (%)
Male:					
Apical	10 yrs.	94	21	73	77.6
	15 yrs.	87	7	80	91.9
Aortic	10 yrs.	21	4	17	80.9
	15 yrs.	20	1	19	95.0
Total	10 yrs.	115	25	90	78.2
	15 yrs.	107	8	99	92.5
Female:					
Apical	10 yrs.	59	19	40	67.6
	15 yrs.	50	4	46	92.0
Aortic	10 yrs.	13	8	5	38.4
	15 yrs.	11	1	10	90.9
Total	10 yrs.	72	27	45	62.5
	15 yrs.	61	5	56	91.8

Relation of Sex and Location of the Murmur to Mortality.   In Table 3 mortality for both 10 and 15 year follow-up periods is considered with respect to the sex of the patient and the location of the murmur.

At the end of 10 years the males had a death rate considerably higher than the females, 78.2% as compared to 62.5% having died.   By the end of 15 years this difference had disappeared, the mortality among the females was 91.6% and for the males 92.5%.

It is evident that in this series the 10 year expectancy of females was definitely better than that for males.   This existed irrespective of the location of the murmur though the difference was more marked in those with aortic murmurs.   In females with aortic murmurs only 38.4% succumbed within 10 years, while 80.9% of the males died. In those patients with apical murmurs the mortality among females was 10% less than that for the males.

When the relation of the location of the murmur to mortality was considered it was found that during the first 10 years the death rate was higher for those with apical murmurs than for those with aortic murmurs.   Of the 153 patients, 113 (73.8%) with apical murmurs had died, while only 22 (59.6%) of the 34 patients with aortic murmurs had succumbed.   However, as with the factor of sex, by the end of 15 years this difference had been erased.   At the end of this period 91.9% of those with apical murmurs and 92.9% of those with aortic murmurs were dead.

In view of the high mortality among these patients it is pertinent to comment on the longevity.   Among those with degenerative heart disease only 2 died under the age of 50.   All others were known to have lived beyond this age.   Of the 40 patients, 16 with rheumatic heart disease lived beyond 50 years of age.   In 10, death came after this age, while 6 were living beyond 50 when last heard from.   Death came before the age of 50 to 15, while 9 were living at an age less than 50. Among the cases with heart disease of unknown etiology, 6 of the

12 deaths occurred after 50, while 5 of the patients were known to have been living beyond this age. Six patients died before they reached 50, while 3 were living at an age less than 50 at the time of our last information. The one patient with luetic heart disease was living beyond the age of 50, while 1 patient with congenital heart disease was living at less than this age when last heard from. The other case of congenital heart disease died before reaching 50.

In summary, of the 187 cases, 150 lived beyond 50 years of age, 13 were living at an age under 50, while only 24 of the 155 deaths occurred before 50.

Two facts regarding those patients who were living at the end of the two follow-up periods are worthy of mention. First, as to etiology of those 52 who survived 10 years, 21 were rheumatic, 19 were degenerative, 10 of questionable etiology, 1 congenital and 1 luetic. Among the 13 patients who survived 15 years, 8 were rheumatic, 2 were degenerative, and 3 were of questionable etiology. Secondly, the average age at the time of the first examination for those who survived 10 years was 42, while the average was 37 for those who survived 15 years. This seems significant in view of the fact that the average age for the group as a whole was 54 years.

The Relation of Heart Size to Mortality in Patients With Loud Systolic Murmurs. Heart size is established as one of the most important determinations in the practice of cardiology, likewise there has been much attention paid to the correlation of heart size and prognosis. It is generally accepted that the greater the degree of cardiac enlargement the more grave is the outlook.

As previously stated of our total group of 187 cases, 155 are known to have died while 32 were living at the time of our last information 10 or more years after first being seen. In Table 4 we have shown the relation of heart size to mortality and also have included the factors of location of the murmur and etiology of the heart disease present.

TABLE 4.—THE RELATION OF HEART SIZE TO 15 YEAR MORTALITY IN PATIENTS WITH LOUD SYSTOLIC MURMURS

	No enlargement		Slight enlargement		Moderate enlargement		Marked enlargement	
	Dead	Living	Dead	Living	Dead	Living	Dead	Living
Degenerative:								
Apical	18	2	23	1	33	2	25	0
Aortic	8	1	2	0	5	0	3	1
Rheumatic:								
Apical	7	9	9	4	2	0	1	0
Aortic	3	1	1	1	1	0	1	0
Unknown:								
Apical	5	4	2	2	2	1	0	0
Aortic	0	1	0	0	2	0	1	0
Congenital:								
Apical	0	1	0	0	0	0	0	0
Aortic	1	0	0	0	0	0	0	0
Luetic:								
Apical	0	0	0	0	0	0	0	0
Aortic	0	1	0	0	0	0	0	0
Total patients	42	20	37	8	45	3	31	1
Mortality, %	67.7		82.2		93.7		96.8	

In the older patients with degenerative heart disease heart size had little bearing on the high mortality which was present in this group. However, when it is considered that 5 of the deaths among those with normal heart size were non-cardiac and in 7 others the cause of death was not determined, it indicates that normal heart size probably portends a better prognosis.

This is even more striking among those with rheumatic heart disease and normal heart size. While one-half of these people are dead, only 3 of the 10 deaths were due to heart failure. Subacute bacterial endocarditis accounted for 3 and 4 died of non-cardiac causes. There was apparently a definite relationship between heart size and mortality among those patients with rheumatic heart disease. This relationship seems to be present among those with heart disease of unknown etiology though the number is small. Among the 5 deaths occurring in patients with normal heart size, the cause was not known in 2.

Though the number of patients with aortic murmurs is too small for a definite conclusion, our findings would indicate that the rather poor outlook is relatively unaffected by the heart size when the patient is first seen.

The summary of mortality per cent at the bottom of Table 4 shows a definite increase in mortality with increasing heart size. This is even more striking when it is pointed out that only 21 of the 42 deaths among those with normal heart size were known to be due to cardiac failure. It would seem that a normal heart size justifies a better prognosis, this being particularly true if the heart disease is of rheumatic etiology.

Distribution of Deaths. It has been mentioned previously that all of the 155 deaths known to have taken place occurred within 15 years.

In Table 4 the distribution of these deaths has been indicated, expressed in per cent of total deaths occurring during each year. It will be noted that the exact date of death was unknown in 7 cases; however, 3 of these were known to have died within 10 years, and the other 4 within 15 years of the first examination.

Seventy-four (47.7%) of the deaths occurred within the first year. Sixty (81%) of these were among the degenerative group, 13 (17.5%) had rheumatic heart disease, and in 1 the etiology of the heart disease was unknown.

When the total number of cases in each etiologic group is considered there is no appreciable difference in mortality between the degenerative and rheumatic types of heart disease during the first year, 51.9% of the degenerative and 52% of the rheumatic deaths having occurred then. By the end of 3 years 70.8% of the total deaths had been accounted for; 73.5% of the deaths of the degenerative group, 64% of the rheumatic, and 50% of those of the group of uncertain etiology had taken place. In succeeding years the mortality was greatly diminished.

The occurrence of such a large per cent of the deaths within 3 years and of only 8 of these known to be non-cardiac in nature, indicates the severity of the heart disease which existed among these patients. The fact that most of these patients were seen in a consulting cardiac

practice may have some bearing since consultation is most usually obtained for patients who are regarded as having a serious disease. This early mortality cannot be entirely accounted for on this basis, however, since a considerable number of those who died relatively early had mild or no symptoms when first seen. It is interesting to note that the majority of the non-cardiac deaths, 12 of the 20, occurred after 3 years had elapsed.

TABLE 5.—LOUD SYSTOLIC MURMURS. DISTRIBUTION OF DEATHS BY YEARS AND ETIOLOGY

Survival period	Degenerative	Rheumatic	Unknown cause	Congenital	Luetic	Total	Deaths (%)
Total deaths . . .	117	25	12	1	0	155	100 0
Died within 1 yr. . .	60 (3)	13 (1)	1	0	0	74	47 7
1 to 2	14	3 (1)	3	1	0	21	13.5
2 to 3	12 (3)	1	2	0	0	15	9 6
3 to 4	3 (1)	1 (1)	1	0	0	5	3 2
4 to 5	5	0	0	0	0	5	3 2
5 to 6	3 (3)	0	1	0	0	4	2 5
6 to 7	2 (2)	0	1	0	0	3	1 9
7 to 8	2 (1)	0	0	0	0	2	1.2
8 to 9	0	1	0	0	0	1	1 6
9 to 10	2 (1)	0	0	0	0	2	1 2
? date	2	0	1	0	0	3	1 9
Total at 10 yrs. . .	105	19	10	1	0	135	87 0
10 to 11	6	4	1	0	0	11	7 0
11 to 12	3 (1)	0	0	0	0	3	1 9
12 to 13	0	0	0	0	0	0	
13 to 14	0	0	0	0	0	0	
14 to 15	1 (1)	0	1	0	0	2	1 2
? date	2	2 (1)	0	0	0	4	2 5

Number in parentheses indicates patients who died of non-cardiac causes.

Consideration of Various Factors in Relation to Prognosis. It would be valuable if certain factors could be determined which would aid in the prognosis of the individual case. With this in mind a comparison was made between some of the characteristics of those patients who died and those of a group of patients who, when last heard from, were living with either mild or no cardiac symptoms 10 to 21 years after they had come under observation. There were 28 such patients still alive; 4 others were eliminated because of the severity of their symptoms.

The average elapsed time from the date of the first examination was 13.8 years for the 28 cases.

Age again appears to be an important factor since the average age of these patients was 33.9 years when first seen. Ages varied from 3 to 69 years, there being 4 patients over 50, and 7 under 20. When compared with the average age of 60 for those patients who later died, there is a marked difference.

Fifteen of those living were males, while 13 were females. This is a somewhat higher proportion of females than was present among the patients who died.

Rheumatic etiology also is again emphasized in this comparison. Only 16.1% of those who died had this type of heart disease, while it

was present in 46.4% of those who were living. Heart disease of unknown etiology was present in 25%, and degenerative heart disease in only 21.4%. There was 1 case of luetic and 1 of congenital etiology. The incidence of "degenerative" heart disease among those who died was 75.4%, while 7.7% had heart disease of unknown etiology.

Heart size would appear to be of some value in prognosis since only 8 of the 28 living patients had enlarged hearts when first examined, while 72.9% of those who died showed enlargement. Furthermore only 1 of the survival group had more than slight enlargement, while of those who died 31 showed marked enlargement, 45 moderate, and 37 slight enlargement, 42 no enlargement. While cardiac enlargement of more than slight degree is an ominous prognostic sign, normal cardiac size does not give much assurance since in about one-fourth of those in this series who died cardiac size had been normal.

With respect to the characteristics of the murmurs in the two groups, there was only one difference noted. Masking of the first sound at the point of maximum intensity of the murmur was noted only once in the living, while it was not an uncommon finding in those with apical murmurs who died. In other respects the description of the murmurs in the two groups was widely variable except that all murmurs were uniformly loud and of long duration.

In 14 of the living patients a detailed description of the murmur was given at the time of the last examination. In 9 the murmur was unchanged and in 2 the murmur of mitral stenosis had developed. In 1 case the murmur was described as being of moderate intensity after 15 years. Two young men were accepted for service in the armed forces during the present emergency, indicating a probable decrease in the intensity of the murmurs. There was no case in which the murmur was known to have disappeared. The development of diastolic murmurs was apparently rare in this series of cases, being recorded in 4 who later died, in addition to 2 instances mentioned previously; however, detailed descriptions of the murmurs were not frequently enough recorded terminally for us to be certain of this point.

The location of the murmur had no significance in prognosis so far as these two groups of cases were concerned since the murmur was apical in location in 78.6% of the patients who were living, and in the same location in 81.3% of those who died.

Palpable thrills were recorded in 23 of the 187 cases when first examined and were noted later in 2 cases. The thrill was at the apex in 9, and at the aortic area in 16. Among the 28 patients who were living there were 5 who presented thrills, 3 at the apex and 2 at the aortic area. It thus happens that thrills were proportionally more frequent among those patients who were living.

It must be concluded that there was found no great basis for accurate prognosis, but rather simple trends. Among those who succumbed within 10 years, the male sex predominated. It is apparent too that the younger the patient, the greater number of years he may be expected to survive. Also, closely related to age, is the fact that rheumatic etiology gave a somewhat better outlook. So far as physical

findings are concerned, masking of the first heart sound by the murmur and more than slight cardiac enlargement were unfavorable findings when present. Cardiac symptoms were absent or of insignificant character in all of those patients in the living group when first seen. Confidence in prognosis is not firmly established by our findings, however, since patients not uncommonly died relatively early in whom there were no apparent characteristics which would indicate early death.

Further Discussion. It has been the consensus during recent years that systolic murmurs cannot be dismissed as unimportant. Levine[3] considered all loud systolic murmurs as indicative of cardiovascular disease. Later Freeman and Levine[1] concluded that nearly all murmurs of "Grades 3 and 4" intensity were associated with organic heart disease. Scott[4] states that a systolic murmur in a person over 40 years of age should always be suspected as a sign of heart disease.

Statistics accumulated by insurance organizations have contributed much to support this concept. Starr[5] found that persons having a transmitted apical systolic murmur had a death rate $8\frac{1}{2}$ times the normal. With a history of previous infection this was increased to 15 times the normal death rate. The death rate was 12 times the expected normal in persons having a transmitted aortic systolic murmur. Cardiac enlargement was found further to increase the mortality rate.

Hunter[2] in a study of the relation between cardiac murmurs and death rate obtained some very impressive results. The death rate was at least double the expected normal in persons who had a constant apical systolic murmur which was transmitted to the left. If, in addition, there was slight cardiac enlargement the extra mortality over normal was 134%, and if moderate enlargement was present the extra mortality was 376% over normal. The constant transmitted aortic systolic murmurs were associated with an increase in mortality of 157% above normal. In cases of cardiac enlargement of mild or moderate degree without murmurs, the death rate was 88% above the expected normal.

In the present series of cases the decrease in longevity found in association with loud systolic murmurs was greater than we had anticipated. The degree to which longevity was affected in patients who succumbed is illustrated by the fact that the average length of life after the first examination was 39.2 months in the rheumatic group, 31.5 months in the degenerative group, and in the group of uncertain etiology, 67.2 months.

From our experience it seems that systolic murmurs of this intensity are almost certainly associated with cardiovascular disease. While such factors as anemia, pregnancy, hyperthyroidism, and neurocirculatory asthenia give rise to systolic murmurs, it is doubtful if they often become as loud as the murmurs we are discussing. In only 1 case in this series was there an extra cardiovascular factor which might have been of significance. In 1 female, who had definite organic heart disease, the question of thyrotoxicosis arose. She expired postopera-

tively in a distant hospital following thyroidectomy. It seems very improbable that the endocrine disease, if present, was of any importance in causing the murmur.

Although a loud systolic murmur of rheumatic etiology in a relatively young individual with no cardiac symptoms usually has a relatively good prognosis, examination of those patients who have died shows that the practical application of this conclusion is limited, principally by the tendency to subacute bacterial endocarditis. However barring the occurrence of subacute bacterial endocarditis such a murmur may exist in a young individual for years without impairing health and may even decrease in intensity. But the fact that 6 (24%) of all deaths in our rheumatic group were due to subacute bacterial endocarditis indicates the hazard which these people face even though cardiac compensation is well maintained. In the degenerative group death not uncommonly occurred relatively early even though symptoms were not more than mild when the patients were first seen, and both appreciable cardiac enlargement and masking of the first sound were absent.

There was not a sufficient number of electrocardiograms or post-mortem examinations in this series to make analysis of them worthwhile.

It seems that the observation made by one of us (P. D. W.) in 1927, that the seriousness of the systolic murmur is directly related to its intensity, is supported by this study, but for final conclusions a follow-up analysis of cases with systolic murmurs of slight to moderate intensity is also needed; this other study we hope to carry out when the war permits.

Summary. Determination of the status of 187 private patients who showed loud systolic murmurs, best heard at either the apex or aortic area, without diastolic murmurs, 10 to 21 years after they were first examined resulted in finding that 155 (82.5%) were dead. Death was due to heart disease in 122 (78.7%).

Seventy-four (47.7%) of all deaths occurred within a year after the first examination, while 110 (70.8%) of the deaths occurred within 3 years.

The outlook for the younger patients with rheumatic heart disease was somewhat better than for those with heart disease of "degenerative" or uncertain etiology. In spite of the high death rate only 24 of the 155 deaths occurred under the age of 50. The death rate was lower among females for the 10 year period but equaled that of the males by the end of 15 years. Of the deaths among those with rheumatic heart disease, 24% were due to subacute bacterial endocarditis. Those with larger hearts had a higher mortality. Despite these prognostic trends, however, it is impossible to predict with any high degree of assurance the course of any particular case.

An interesting and important observation is that some cases originally diagnosed as having mitral regurgitation because of a loud apical systolic murmur were later found to have aortic stenosis which in the course of 10 or 15 years tended to precipitate abrupt left ventricular

failure (acute pulmonary edema).   The clue to these cases lies in the fact that the loud, somewhat harsh systolic murmur heard at the apex is also heard at the aortic valve area, although perhaps less loudly. The murmur is primarily an aortic systolic murmur well transmitted to the apex as well as into the neck vessels; a mitral regurgitant murmur is often well heard at the lung bases (and in the left axilla) but not at the aortic valve area.

It is evident that loud systolic murmurs at the cardiac apex or aortic valve area are clinically important even in the absence of diastolic murmurs and of well-marked cardiac enlargement.

REFERENCES

1. Freeman, A. R., and Levine, S. A.:   Ann. Int. Med., 6, 1371, 1933.
2. Hunter, A.:   Am. Heart J., 14, 10, 1937.
3. Levine, S. A.:   J. Am. Med. Assn., 101, 436, 1933.
4. Scott, R. W.:   Proc. Assn. Life Ins. Med. Div. of America, 21, 114, 1934.
5. Starr, J. F.:   South J. Med. and Surg., 95, 647, 1933.
6. White, P. D.:   Am. J. Med. Sci., 174, 731, 1927.

MAGNESIUM SULFATE IN PAROXYSMAL TACHYCARDIA*

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Although the cardio-inhibitory action of magnesium salts has been known for a long time,[1,2,3] it is rarely employed for therapeutic purposes in cardiac disease.   Beneficial effects should be expected in disturbances resulting from augmented myocardial irritability or increased stimulus formation.

In 1930, Seekles employed magnesium chloride intravenously to prevent arrhythmias evoked by intravenous injections of calcium chloride, given to cows suffering from milk fever or grass staggers (grass tetany).   The combination of magnesium chloride and calcium chloride yielded better results.   In 1935 Zwillinger recommended magnesium sulfate by vein for the treatment of premature contractions and paroxysmal tachycardias.   A patient lost consciousness and appeared dead when many multifocal extrasystoles and ventricular flutter occurred after the intravenous injection of 0.25 mg. of strophanthin; an intracardiac injection of 10 cc. of a 15% solution of magnesium sulfate revived him, the flutter subsiding and the extrasystoles vanishing for a short time.   On the basis of this experience the author employed 10 to 15 cc. of a 15% solution of magnesium sulfate, in 1 instance even 10 cc. of a 30% solution, in patients suffering from paroxysmal auricular tachycardia; in all cases the tachycardia imme-

diately stopped and sinus rhythm was restored. No effect was obtained with this remedy in 3 cases of auricular flutter and 2 of auricular fibrillation.

Medical literature is relatively silent on the therapeutic effect of magnesium salts on paroxysmal tachycardia. On the basis of animal experiments, Smith, Winkler and Hoff state that "it seems rather doubtful whether the small doses recommended have much effect on cardiac rhythm." The present paper reviews our experience with 11 patients treated by an intravenous injection of magnesium sulfate.

TABLE 1.—RESULTS OF INTRAVENOUS INJECTIONS OF MAGNESIUM SULFATE

No.	Name	Age	Clinical diagnosis	Type of tachycardia*	Dosage of MgSO₄	Effect on tachycardia	Changes after injection
1	W. H.	72	Cor. scl.	p.a.t.	20 cc. of 20% sol.	+	Ventricular extrasystoles
					10 cc. of 10% sol.	−	
2	D. H.	50	Cor. scl.	p.v.t.	20 cc. of 10% sol.	+	
			Hypert., auric. fibril.	..	" " " " "	+	
3	V. J.	52	Gen. arterioscl.	p.a.t.	20 cc. of 20% sol.	+	Prolongation of P-R, ventricular extrasystoles
			Hypert., hemiplegia	..	" " " " "	+	Prolongation of P-R
					" " " " "	+	
					" " " " "	+	
4	J. G.	53	Pericard., Myocard.	a.f.	" " " " "		Alteration of flutter waves and a.v. conduction disturb., ventricular extrasystoles
5	H. S.	52	Luetic aortitis	p.a.t.	" " " " "	+	
6	M. W.	39	Rheum. mitral lesion	p.a.t.	20 cc. of 10% sol.	−	
					20 cc. of 20% sol.	+	Prolongation of P-R
					" " " " "	+	Prolongation of P-R
7	B. W.	42	Luetic aortic insuf.	p.a.t.	15 cc. of 10% sol.	−	
					20 cc. of 10% sol.	−	
					" " " " "	+	
8	V. K.	70	Rheum. mitral lesion	p.v.t.	" " " " "	−	
9	M. A.	60	Rheum. mitral lesion	p.a.t.	" " " " "	−	
10	D. S.	27	No organic ht. dis.	p.a.t.	" " " " "	−	
11	B. O.	51	No organic ht. dis.	p.a.t.	" " " " "	−	

* p.a.t. = paroxysmal auricular tachycardia; p.v.t. = paroxysmal ventricular tachycardia; a.f. = auricular flutter.

Observations. The results are summarized in Table 1. Twenty injections were given to 11 patients whose age varied between 27 and 72. Most of them had organic heart disease and some severe decompensation. Eight had paroxysmal auricular tachycardia, 2 paroxysmal ventricular tachycardia and 1 auricular flutter. Excluding the last, success was obtained in 6 of the 10 patients with paroxysmal tachycardia. In 1 instance each of 4 attacks was abolished by magnesium sulfate. Failures were limited to those individuals who received a 10% solution although this concentration sufficed for 1 patient with paroxysmal ventricular tachycardia and once in a case of paroxysmal

auricular tachycardia. Increases of volume of the solution seemed less important in obtaining good results than an increase of concentration.

All patients complained of a sensation of intense heat immediately following the injection and most of them perspired and became flushed;[5] some complained of dizziness; nausea was frequent but vomiting was rare. General weakness was frequently noted for a short time after the injection.

In most cases the tachycardia ceased just before the injection was completed or immediately thereafter. Usually the attack stopped suddenly without any change in the electrocardiogram. This is evident in Figure 1*A* (Case 6). In this instance an auricular tachycardia with a rate of 186 disappeared during the injection of 20 cc. of a 20% solution of magnesium sulfate. If the effect is not immediate, none should be expected afterwards. In this respect the effect of magnesium sulfate resembles that of quinine or quinidine administered by the same route since the latter also acts at once or not at all. This also emphasizes the importance of the concentration.
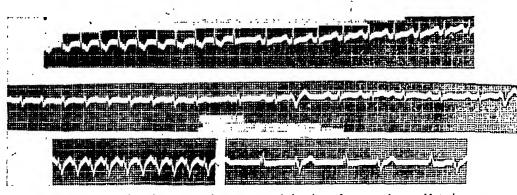
Fig. 1.—*A* shows the effect of an intravenous injection of magnesium sulfate in a case of paroxysmal auricular tachycardia; *B* shows a prolongation of the auriculoventricular conduction time and ventricular extrasystoles immediately after the injection of this agent in a case of paroxysmal auricular tachycardia; in *C*, a paroxysmal ventricular tachycardia disappears after the intravenous injection of magnesium sulfate.

In 3 patients the auriculoventricular conduction time of the sinus rhythm was lengthened immediately after the attack. The prolongation amounted to 0.02 to 0.05 second and persisted for a few seconds. This is exemplified by Figure 1*B* (Case 3). In this case of paroxysmal auricular tachycardia, each of 4 attacks were abolished by an injection of 20 cc. of a 20% solution of magnesium sulfate. The prolongation of the P–R interval however appeared only twice. A similar prolongation of the auriculoventricular conduction time was observed after 1 injection in Case 4 and 1 in Case 6.

Ordinarily the attack subsided abruptly without intermediate changes of rate or rhythm. In 3 cases, however, the rate of the tachycardia gradually slowed before it disappeared. In Case 3 it fell from 188 to 153 after each of 2 injections; in Case 5 it changed from 171 to 111 and in Case 6, 1 injection caused it to fall from 181 to 166 in 1 attack and from 193 to 176 in another.

Ventricular extrasystoles were noted after the injection (Fig. 1*B*) in 3 instances (Cases 1, 3 and 4). In 2 of them paroxysmal auricular tachycardia was present while auricular flutter was present in the other. In none of these cases were the ventricular extrasystoles of a type ever recorded in these patients previously.

The action of magnesium sulfate in a case of ventricular tachycardia is seen in Figure 1*C*. This 50 year old patient suffered from coronary sclerosis and auricular fibrillation. The first part of Figure 1*C* shows the ventricular tachycardia before, and the second part the fibrillation with single ventricular extrasystoles immediately after the injection of 20 cc. of a 10% solution of magnesium sulfate.
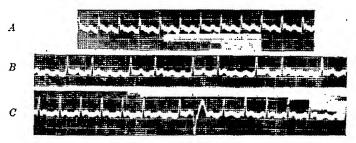
Fig. 2.—The tracings (Lead II), show the changes in the form of the F waves, ventricular extrasystoles and increased auriculoventricular block after the injection of magnesium sulfate in a case of auricular flutter.

The injection of 20 cc. of a 20% solution of magnesium sulfate did not produce any change in the flutter mechanism or the flutter rate in the single trial in this series. The shape of the F waves changed slightly presumably due to an intra-auricular block and the continuous 2:1 auriculoventricular block changed to a variable block with short periods of 4:1 block. This patient also had ventricular extrasystoles only when the magnesium preparation was given. The regular flutter with 2:1 block before the injection is evident in Figure 2*A*; Figure 2*B* and 2*C* show the changes in the F waves, the greater auriculoventricular block, and a ventricular extrasystole shortly after the injection. The electrocardiogram reverted to the appearance of Figure 2*A* within 4 minutes.

Discussion. The initial treatment of any attack of paroxysmal tachycardia should consist of a trial of the various vagal reflexes since these simple measures suffice to abolish the attack in a large percentage of the cases. Medicinal therapy is justified only when these reflexes (carotid sinus, bulbar, gag reflex, the Valsalva experiment) prove useless. Moreover the oral administration of quinidine is often successful although several hours or a few days may lapse before the result is obtained. It is not unusual, however, to encounter individuals who do not tolerate drugs of the quinine group although the attack must be abolished immediately owing to the development of severe anginal pain,[12] decompensation, or for some other reason. While the intravenous injection of quinine (quinidine) often yields an immediate and

satisfactory response, it is not always innocuous;[7] untoward symptoms have also appeared after the injection of mecholyl.[10]   Therefore, the intravenous use of magnesium sulfate merits a definite place among these drugs in the medicinal management of these disorders.

The effect of bivalent electrolytes on cardiac automatism and stimulus formation varies markedly.   Barium causes a very pronounced and stormy increase of stimulus formation; calcium acts similarly but is weaker and the action becomes evident only after much larger doses.   Magnesium is antagonistic to calcium and inhibits stimulus formation; it disappears quickly from the blood but increased amounts cannot be recovered from the heart after an injection.   Nevertheless a cumulative effect has been reported after injections are repeated at short intervals so that caution should be exerted in regard to dosage, if a second injection is given after a short interval.[2]

The appearance of extrasystoles under the influence of an inhibitory drug such as magnesium does not seem to have been previously observed in man but has been reported in the experimental animal.[4,9] The paradoxic occurrence of extrasystoles and even paroxysmal tachycardias after the administration of substances which ordinarily suppress them is a common observation; digitalis, potassium and quinine in moderate doses suppress extrasystoles while excessive amounts may be responsible for extrasystoles and even ventricular fibrillation.

The development of disturbed auriculoventricular conduction following administration of magnesium salts had to be anticipated on the basis on its depressing action and has been observed in animals.[11]   In our patients it lasted only for a few seconds when the concentration of magnesium in the blood was high.   While auriculoventricular conduction disturbances may be seen during or immediately after a tachycardia when the conduction system is fatigued, the observation of a similar disturbance during flutter, at the height of the magnesium effect, indicates that this must be attributed to the drug itself.

No untoward effects were encountered in our series.   Some observers have employed a 30% solution without any accident.[14,15]   Winkler, Smith and Hoff report a fatality after the injection of 30 cc. of a 25% solution without providing any details.[13]   However, magnesium salts have often been given in concentrations of 10% to 30% by other workers for coronary sclerosis, angina pectoris and so forth without evil results.   We would hesitate to employ the drug when marked myocardial damage is obvious, marked intraventricular conduction disturbances or gallop rhythm are present.   Since the concentration in which the drug reaches the heart is important for the accomplishment of an effect, the injection should not be given too slowly; theoretically injection of higher concentrations might damage the heart if it is given too rapidly so that a moderately rapid injection is suggested.   About 30 seconds should be taken for the injection.   The employment of 15 to 20 cc. of a 20% solution promises greater success than larger volumes of a 10% solution.   No important change of sinus rhythm followed the amounts given by us.   The difference of response of a normal automatic center and an abnormal extrasystolic center is a

matter of common observation and the difference in doses necessary for dogs and man has been previously emphasized.[6]

While we can confirm the observation that digitalis extrasystoles are abolished by magnesium sulfate, the effect lasts only for a few minutes.[15] Perhaps some paroxysmal tachycardias of multifocal origin which appear after large doses of digitalis or injections of strophanthin and which, unfortunately, sometimes change into ventricular fibrillation may be influenced by injections of magnesium sulfate whereby a dangerous accident might be averted.

Conclusions. The effect of intravenous injections of magnesium sulfate in 10 cases of paroxysmal tachycardia and 1 case of flutter was studied.

The injection of a 10% solution was beneficial in 3 out of 8 attacks, while a 20% solution succeeded in 8 out of 8 attacks. Consequently the use of a 20% solution is advocated.

Disturbances of conduction and ventricular extrasystoles appear for a short time after the injection. The rate of the paroxysmal tachycardia frequently diminishes before the tachycardia disappears.

In the doses and with the indications discussed, the intravenous injection of magnesium sulfate may be recommended as a useful therapeutic procedure in paroxysmal tachycardias.

REFERENCES

1. CARLSON, A. J.: Am. J. Physiol., 16, 378, 1906.
2. MATTHEWS, S. A., and JACKSON, D. E.: Am. J. Physiol., 19, 5, 1907.
3. MELTZER, S. J., and AUER, J.: Am. J. Physiol., 21, 400, 1908.
4. MILLER, J. R., and VAN DELLEN, T. R.: J. Lab. and Clin. Med., 26, 1116, 1941.
5. PINES, N.: Lancet, 1, 577, 1933.
6. ROTHBERGER, C. J., and ZWILLINGER, L.: Arch. f. exper. Path. u. Pharmakol., 181, 301, 1936.
7. SCHERF, D., and BOYD, L. J.: Clinical Electrocardiography, St. Louis, C. V. Mosby Co., 1940.
8. SEEKLES, L., SJOLLEMA, B., and VAN DER KAAY, F. C.: Tijdschr. v. diergeneesk., 57, 1229, 1285, 1341, 1930.
9. SMITH, P. K., WINKLER, A. W., and HOFF, H. E.: Anesthesiology, 3, 323, 1942.
10. STARR, I., JR.: AM. J. MED. SCI., 186, 330, 1933.
11. VAN DELLEN, T. R., and MILLER, J. R.: J. Lab. and Clin. Med., 24, 840, 1939.
12. WHITE, P. D., and CAMP, P. D.: Am. Heart J., 7, 581, 1932.
13. WINKLER, A. W., SMITH, P. K., and HOFF, H. E.: J. Clin. Invest., 21, 207, 1942.
14. YASKIN, H. E.: Arch. Neurol. and Psychiat., 46, 81, 1941.
15. ZWILLINGER, L.: Klin. Wchnschr., 14, 1429, 1935.

CRITERIA FOR DIFFERENTIATING DEEP Q₃ ELECTROCARDIO-GRAMS FROM NORMAL AND CARDIAC SUBJECTS*

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PARDEE[11] proposed criteria for evaluating the significance of a Q wave in Lead III of the electrocardiogram (Ecg) and a number of workers

on the basis of his criteria have reported the incidence of significant Q_3 waves in individuals with diseased and normal hearts. It is generally recognized that such Q_3 waves occur with much greater frequency in individuals with heart disease than in normal persons. The Ecg's of patients with heart disease present significantly deep Q_3 waves in from 4.4% to 15% of various series,[1,6,11,18] while only 0.47% of tracings from a series of 1694 normal individuals collected from the literature showed this finding.[1,4,7,8,11,13,15] Significantly deep Q_3 waves are most often associated with arteriosclerotic heart disease and in particular with myocardial infarction.[10,12,19] When a deep Q_3 wave appears in the Ecg of individuals without apparent heart disease the interpretation of the finding may be a cause for confusion. It is known that factors causing the heart to assume a more transverse position will often produce a deep Q_3 wave in the Ecg. This is true whether the heart is in the transverse position normally[20] or as a result of pregnancy,[11,16] ascites or gaseous abdominal distention,[15] pneumoperitoneum,[5] or pulmonary disease.[9] Deep inspiration which depresses the diaphragm causes the Q_3 to become less deep in such cases[17] and relief of abdominal distention or ascites[20] often results in the disappearance of the deep Q_3. Precisely how cardiac position effects this change in the Ecg and whether other factors may act similarly are not known, although the practical fact remains that a deep primary negative deflection in QRS_3 is not necessarily evidence of myocardial damage.

The question naturally arises as to whether a deep Q wave has the same origin and meaning as a small Q wave in Lead III. Shookhoff and Douglass[14,15] investigated the problem by studying the time relationship of normal and deep Q waves. They found that all of the Q waves in limb leads in normal tracings corresponded in time with reasonable accuracy. In tracings with significant Q_3 waves the time occupied by the Q_3 wave was not identical with that of Q_1 and Q_2. In most instances the Q_3 corresponded in time with parts of R_1 and R_2. Bayley[12] suggested the use of the prolongation of Q_3 as a test of its significance.

Attempts have been made to establish other criteria which would increase the accuracy of interpretation of Ecgs with deep Q_3 waves. Pardee[11] and Durant[3] have found that if the Q_3 is 50% or more of the highest R wave the incidence of organic myocardial disease is higher than when the Q_3 is smaller. The presence of a Q_2 wave of 25% or more of the highest R in addition to the Q_3 was associated with an increased incidence of coronary disease in Durant's series.[3] In Bayley's study,[2] most of the cases of myocardial infarction occurred in the group showing a Q_2 of 1 mm. or more in addition to a prolonged Q_3. The significance of changes in the Q_3 due to respiration has been investigated by Videla[17] who found that a greater decrease in size during deep inspiration occurred in individuals without organic heart disease. The known influence of cardiac position on the occurrence of the deep Q_3 may also be considered in interpretation to a limited extent; thus, if a deep Q_3 is found in a tracing which is otherwise nor-

mal, the demonstration that the heart is transversely placed makes the finding of less significance.

The essential difficulty in the interpretation of Ecgs with deep Q waves in Lead III arises in those instances in which the other features of the tracings are within normal limits. The present study is an attempt to find criteria which will permit the differentiation of such tracings from normal and cardiac subjects.

Material. In our file of Ecgs there were records of 102 hospitalized patients which had a Q wave in Lead III conforming to Pardee's[11] criteria for significance. The study was limited to in-patients because the thoroughness of their investigation made the clinical diagnoses more certain than in the case of out-patients. The cardiac diagnoses for the 102 individuals are given in Table 1.

TABLE 1.—CARDIAC DIAGNOSES IN 102 Q₃ ECG'S

Diagnoses	No. of cases	% of total
Myocardial infarction	44	43.2
Arteriosclerotic heart disease	15	14.7
Hypertensive heart disease	14	13.7
Rheumatic heart disease	2	2.0
Unclassified heart disease	1	1.0
Total organic heart disease	76	74.6
Hypertension	7	6.8
No heart disease	19	18.6
Total	102	100.0

The data on the Ecgs tabulated below were secured from one tracing for each patient. Since some patients, particularly those with myocardial infarction, had many tracings, it was important that the tracing used for each patient be chosen at random. This was done before the actual tracings were studied.

It is seen from Table 1 that 19 of 102 patients with deep Q₃ Ecgs had no evidence of heart disease. This is a higher incidence of normal subjects than in most series of deep Q₃ tracings reported. It is almost identical, however, to the 20% incidence reported by Ziskin[20] from similar material in a Veterans' Hospital. The difference in the frequency of normal subjects in our series of Q₃ tracings and those reported is to be found in the nature of the population from which the tracings were drawn. If more of the tracings in our complete Ecg file represented normal subjects than in the files of other workers it would be expected that we would find more deep Q₃ tracings in normal individuals. This is apparently the case. By sampling methods we found that only 37% of our in-patients who had Ecgs had heart disease. From the data of Ashman and his associates[1] we have computed that 82% of the tracings in their file represent patients with heart disease. This difference is to be expected because of the many routine examinations done for compensation rating purposes in Veterans' Administration Facilities. Our Ecg file contained records of 7800 hospitalized patients of whom 63% (4920) had no heart disease. Since

19 of the patients without heart disease had deep Q_3 tracings the incidence of this finding in normal (non-cardiac) subjects is 0.39%. This value is in fairly good agreement with the figure of 0.47% computed from the data in the literature.

Analysis of Tracings. *The T Wave.* Negative or diphasic T waves in Leads I, I and II and III, or II and III were found in 52 (68%) of the records from patients with organic heart disease with deep Q_3 tracings. As is to be expected, T wave abnormalities were found most often in Leads II and III in association with the deep Q_3. Twenty-nine records of the organic heart disease group had diphasic or inverted T waves in Leads II and III. Ten tracings had such abnormal T waves in all of the limb leads. In 6 tracings the T waves were abnormal in Leads I and II and in 7 in Lead I alone. In none of the tracings from normal or hypertensive subjects were the T waves abnormal. In 5 records in which the limb leads were normal except for the deep Q_3 the chest lead CF_4 had a diphasic or inverted T wave. In 19 records of the organic heart disease group the deep Q_3 was the only abnormality. These will be compared with 19 records of the normal group.

The Q_3 Wave. The records were classified by the depth of the Q_3 in relation to the highest R wave and the results are tabulated in Table 2. Q_3 waves of 100% or more of the highest R wave occurred in 16 cases and only in the group with organic heart disease. In the group with organic disease 42% of the records had Q_3 waves of 75% or more of the highest R, while in the non-cardiac group only 16% had Q_3 waves of this magnitude.

TABLE 2.—Q_3 AS PER CENT OF HIGHEST R WAVE

Highest R wave, %	Number of cases				
	25–49	50–74	75–99	100+	75+
Myocardial infarction	10	11	10	13	23
Arteriosclerotic heart disease	7	3	2	3	5
Hypertensive heart disease	9	3	2	..	2
Rheumatic heart disease	1	..	1	..	1
Unclassified heart disease	..	..	1	..	1
Total organic heart disease	27	17	16	16	32
Hypertension	5	2			
No heart disease	13	3	3	..	3

The Q_2 Wave. A Q wave in Lead II of 1 mm. or more was found in 4 of the 19 (21%) cases of the normal group (Table 3). None of the Q_2 waves in this group was deeper than 3 mm. In the organic heart disease group there were 51 records (67%) in which the Q_2 was 1 mm. or more in depth. In 7 of these the Q_2 wave was greater than 3 mm.

TABLE 3.—Q_3 WAVES OF 1 MM. OR GREATER IN DEEP Q_3 SERIES

Diagnoses	Number of cases						No.	% of total
	1 mm.	2 mm.	3 mm.	4 mm.	5 mm.	6 mm.		
Organic heart disease	20	13	11	3	3	1	51	67
Hypertension	1	..	..	..	..	..	1	14
No heart disease	1	2	1	..	..	..	4	21

The T Wave in Leads I and CF₄.   It is a common observation that posterior heart wall damage with a Q_3 T_3 Ecg pattern is often accompanied by an increase in amplitude of the T wave in Leads I and CF_4. The amplitude of the positive T waves in these leads was, therefore, studied.   The data on the height of the waves is given in Tables 4 and 5.   In the normal group there were no T_1 waves greater than 2 mm. while in 10 cases of the organic heart disease group there were T_1 waves of 3 mm. or more.   A similar partial differentiation was possible by utilizing the data on T_4 wave amplitude.   In 4 cases (21%) of the normal group there were T_4 waves of 4 mm., or more, while in 24 (32%) of the organic heart disease group there were waves of this magnitude.

TABLE 4.—HEIGHT OF POSITIVE T_1 WAVES IN DEEP Q_3 RECORDS

Diagnoses	<1 mm.	1 mm.	2 mm.	3 mm.	4 mm.	5 mm.	3+ mm.
Organic heart disease	7	26	10	6	2	2	10
Hypertension	1	3	1	2	..	..	2
No heart disease	3	12	4	..	..	..	0

TABLE 5.—HEIGHT OF POSITIVE T_4 WAVES IN DEEP Q_3 RECORDS

Diagnoses	<1 mm.	1 mm.	2 mm.	3 mm.	4 mm.	5 mm.	6 mm.	7 mm.	8 mm.	14 mm.	4+ mm.
Organic heart disease	4	11	7	7	13	1	2	6	1	1	24
Hypertension	.	2	1	2	..	..	..	..	..		0
No heart disease		4	5	2	1	3	.				4

Criteria for Differentiating Normal and Abnormal Q_3 Ecgs.   When the Q_3 electrocardiogram contains abnormal T waves it may be concluded that the deep Q_3 is due to organic heart disease.   This is reasonable because the incidence of fortuitously occurring deep Q_3 waves is very small, namely, its incidence in tracings from normal individuals, or about 0.47%.   In instances where the deep Q_3 is the only abnormality a decision as to its significance is often impossible, though the position of the heart as determined by Roentgen ray and the effect of deep inspiration may be of presumptive assistance.   In our series there were 19 records in the organic heart disease group in which the deep Q_3 was the only abnormality either in the limb leads or CF_4. In the 19 cases in the normal group this was, of course, also the case. The 7 hypertensive cases are not included in the following analysis because of the difficulty of deciding with which group they should be considered and they are too few in number to be considered separately.

TABLE 6.—TRACINGS IN WHICH DEEP Q_3 IS ONLY ABNORMALITY
(Number of Proposed Criteria Satisfied by Cases)

Diagnoses	No. of criteria:	0	1	2	3	% in 2 and 3
Organic heart disease	.	3	6	8	2	53
Hypertension	.	4	2	1	..	17
No heart disease		10	7	1	1	11

From the data given in Tables 2 to 5 it is evident that deep Q_3, deep Q_2, high T_1, or high T_4 waves are somewhat more likely to occur

in Q_3 tracings from patients with organic heart disease. However, none of these factors alone can differentiate the abnormal from the normal cases in a sufficient number of instances. It was, therefore, decided to set up criteria involving all four factors and to apply them to those records in which the deep Q_3 was the only abnormality. After study the following criteria were selected: 1, Q_3 of 75% or more of the highest R wave; 2, Q_2 of 1 mm. or more; 3, T_1 of 3 mm. or more; 4, T_4 of 4 mm. or more.

The 38 records which were otherwise normal were restudied to determine how many of the above criteria were satisfied by each. Each record was given a value equal to the number of criteria satisfied. No record satisfied more than 3; many satisfied none. The number of criteria found in each record are given in Table 6 for the normal and abnormal groups. It is seen that the tracings from the abnormal cases tended to satisfy more of the criteria than the others. Only 2 normal cases satisfied more than 1 criterion, while 10 of the 19 organic heart disease cases did. In brief, if an otherwise normal Q_3 electrocardiogram satisfied 2 or more of the criteria proposed, it is more likely to represent a patient with heart disease. Only 11% of our normal group (2 of 19 cases) satisfied as many criteria as 53% of the abnormal group. Therefore, if an otherwise normal Q_3 tracing satisfied 2 to 4 of the criteria suggested it is likely to represent an abnormal heart. If it satisfies fewer than 2 criteria no conclusion can be drawn. It must be emphasized that the figures above are based on a small number of cases and that the findings are, therefore, merely suggestive.

Summary. A series of 102 electrocardiograms (Ecgs) with significantly deep Q_3 waves has been analyzed. Criteria have been suggested to aid in differentiating those from normal and diseased hearts.

REFERENCES

1. Ashman, R., DeLaureal, B. J., Hull, E., and Drawe, D.: J. Lab. and Clin. Med., **18**, 1153, 1932-33.
2. Bayley, R. H.: Am. Heart J., **18**, 308, 1939.
3. Durant, T. M.: Am. J. Med. Sci., **188**, 225, 1934.
4. Edeiken, J., and Wolferth, C. C.: Am. Heart J., **7**, 695, 1932.
5. Elwood, B. J., Piltz, G. F., and Potter, B. P.: Am. Heart J., **19**, 206, 1940.
6. Goldbloom, A. A., and Kramer, M. L.: Med. Clin. North America, **15**, 1345, 1932.
7. Kossman, C. E., Shearer, M., and Texon, M.: Am. Heart J., **11**, 346, 1936.
8. Larsen, K., and Skulason, Th.: Am. Heart J., **22**, 625, 1941.
9. Leverton, W. R.: Ann. Int. Med., **12**, 285, 1938.
10. Pardee, H. E. B.: Arch. Int. Med., **26**, 244, 1920.
11. Pardee, H. E. B.: Arch. Int. Med., **46**, 470, 1930.
12. Parkinson, J., and Bedford, D. E.: Heart, **14**, 195, 1928.
13. Shipley, R. A., and Hallaran, W. R.: Am. Heart J., **11**, 325, 1936.
14. Shookhoff, C., and Douglass, A. H.: Proc. Soc. Exp. Biol. and Med., **31**, 209, 1933-34.
15. Shookhoff, C., and Douglass, A. H.: Ann. Int. Med., **8**, 177, 1934.
16. Strauss, S., and Feldman, L.: Am. J. Med. Sci., **185**, 87, 1933.
17. Videla, J. G.: Rev. argent. de cardiol., **6**, 146, 1939.
18. Williams, F. A.: Am. Heart J., **6**, 723, 1931.
19. Wilson, F. N., Macleod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L.: Heart, **16**, 195, 1933.
20. Ziskin, T.: Arch. Int. Med., **50**, 435, 1932.

DISSECTING ANEURYSM OF THE AORTA

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DISSECTING aneurysm of the aorta is a disease characterized by a splitting of the aorta in the media. Until recently the diagnosis has only rarely been made before death. Holland and Bayley[17] reported 19 cases and in only 2 cases was an antemortem diagnosis made. During the past 3 years 12 instances of dissecting aneurysm were encountered in Grady Hospital, Atlanta, Ga.; an antemortem diagnosis having been made in 10 cases.

The autopsy incidence has been reported from 0.18%[31] to 0.5%[40a] and was found to be 0.7% in 1519 autopsies from 1937 to 1940 in the present series. During this same period, the incidence of saccular aneurysms due to syphilis was 1.51% in this hospital. The greatest number of cases have occurred between the ages of 40 and 60 years. Crowell's review[8] of 215 cases revealed 80% above 40, with an age range of 13 to 95 years. Males are more frequently involved than females.

Pathologic Evidence. Arteriosclerosis has invariably been present. Some observers believe that an intimal tear in an atheromatous area is the initial process. It is striking that the tear is almost never in an atheromatous ulcer, and Mallory[25] states that any tear arising in an ulcer is always localized. Peery[31] cites that only 4 of Shennan's 15 cases showed relation to an atheromatous patch and none was in the base of an ulcer. Medionecrosis aortæ idiopathica cystica, as originally described by Erdheim,[9] is frequently present. Moritz,[28] and more recently Roberts,[34] have reviewed the pathology of this condition. The latter states that 28 cases of dissecting aneurysm have been reported in which the typical cystic degeneration of the media was present. This was noted in 5 of the present group. It seems probable that the infrequency with which it has been reported is due to the fact that careful microscopic studies of sections of the aorta have not been performed. Hypertension is almost invariably present. The increased pressure is certainly an important factor in bringing about the dissection, once the initial process has begun. Strain has been cited as a predisposing cause. Cases have been reported to occur incident to sexual excitement, pregnancy,[21] defecation, walking and lifting objects, and trauma.[35] Syphilis, formerly mentioned as a cause is now thought to play no part in the etiology. The fibrosis in syphilitic aortitis would tend to prevent dissection. Wood and Agnor[44] observed a patient with syphilitic aortitis in which a localized dissection occurred, and they felt that the fibrosis of the media prevented a dissecting aneurysm. Coarctation of the aorta has been noted in a number of cases and Boyd and Werblow[4] made a diagnosis of dissecting aneurysm in one instance. Leary and Weiss[22] produced experimentally a dissecting

aneurysm in a rabbit which was fed cholesterol over a long period of time.

Microscopically, spindle- or oval-shaped areas of cystic degeneration are commonly present. Accompanying this degeneration, is fragmentation of the elastic fibers which may be better visualized with special stains. Rottino[37] has recently reviewed the medial degeneration in 12 selected cases of dissecting aneurysm. He states that it is essentially a disease of the ascending aorta and arch which is characterized by a loss of the muscle tissue, elastic tissue and collagen of the media. There is a lack of inflammatory reaction, and healing occurs by loose scar formation and by regeneration of muscle and elastic tissue. He could not establish the type described by Erdheim.[9]

Dissecting aneurysm occurs, as a rule, in the aorta or one of its main branches, but it has been reported in the pulmonary, cerebral, splenic, and thyroid arteries. More commonly there is a transverse tear in the intima in the first few centimeters of the aorta. The tear in the intima may be located elsewhere in the thoracic or abdominal aorta. When it occurs in such a location, the tear is usually longitudinal or elliptical rather than transverse. The tear may be in the region of the innominate artery or celiac axis, as in 3 patients in the present series. Whitman and Stein,[42] reviewed 5 cases in which there was no tear in the intima. Hamburger and Ferris,[15] and Reisinger[32] reported in each instance 1 case in which an intimal tear was absent. The mechanism of dissection has generally been thought to begin with an intimal tear, however, the latter author questions whether dissection is dependent upon a primary rupture in the intima. It seems quite likely that an intimal rupture is secondary to hemorrhage into the media. The dissection may spread upward and downward in the media, involving the vessels arising from the aorta in its progress. It may cause narrowing of or dissection[11] of the coronary arteries. Occasionally extensive dissection of one of the carotid arteries causes a hemiplegia. Involvement of the lumbar arteries may impair the circulation to the lumbar cord and give rise to neurologic symptoms in the lower extremities. Occlusion of the renal arteries causes hematuria[5] and anuria, while gangrene of the bowel has followed involvement of the mesenteric arteries. The dissection usually involves only a portion of the circular area of the aorta, varying from one-half to two-thirds of the circumference. It may extend down the iliac and femoral arteries and has been reported as far down as the posterior tibial artery.[11] Longitudinal folds causing deep grooves may occur in the ascending portion and transverse arch of the aorta.[45] When the inner and outer layers are completely separated, there may be a sac within a sac. A so-called double-barreled aorta is formed when the dissected channel reënters the lumen of the aorta. Agnor[1] states that this occurs in about 15% of the cases. Gouley and Anderson[13] reported 6 cases of chronic dissecting aneurysm, in 4 of which there was a double-barreled aorta.

The aneurysmal sac is filled with blood in varying stages of organization. One instance has been reported in which blood was absent and the sac was filled with lymph.[42] Localized bulging may occur, being

most often seen in the region of the distal portion of the arch and the proximal portion of the descending aorta. It is here that a rupture through the adventitia frequently results in hemorrhage into the mediastinum and pleural cavity. A rupture through the intrapericardial portion of the aorta is followed by tamponade, the most common cause of death. Baker[2] observed a patient in which the aneurysmal sac compressed the superior vena cava and caused obstruction.

Signs and Symptoms. Pain is usually severe and of sudden onset. It may appear during exertion or while the patient is at rest. It is more commonly sharp and rending in quality, although at times it is crushing and vise-like. The location of the pain is more frequently retro-sternal with radiation towards the neck and then through to the back beneath the left scapula, or rarely beneath the right scapula.[25] Radiation of pain to the arms is unusual, but pain in the neck or mandible is not uncommon, and pain has been reported in the ears.[6a] If the dissection involves the carotid arteries, hemiplegia or visual disturbances may occur. The pain may extend downward to the lumbar region or epigastrium and then to one or both thighs. In those patients in whom the dissection begins in the abdominal aorta, the pain is felt first in the lumbar region or epigastrium. The excruciating pain may last only a few minutes, to be replaced by a more constant dull aching pain, lasting several hours to days. Infrequently, little or no pain may be experienced.[13,15,19,43] In 2 patients of the present group, there was no pain.

There is frequently a transient period of shock, but usually the blood pressure returns to a normal or more commonly to a high level. Vertigo and syncope are common and, at times, may be the most prominent complaints. Hemoptysis has been recorded.[6b] Nausea and vomiting are rarely absent. Diarrhea may follow involvement of the mesenteric vessels and occult blood may be found in the stool in such cases. A gruel-like material is at times seen in the bowel when the mesenteric vessels are involved. In 3 patients in the present group, there was a complaint that the skin felt "hot all over," although the body temperature was normal. Middleton[37] has suggested that this may be due to spontaneous periarterial sympathectomy such as described by Hamburger and Ferris[15] in an attempt to explain the increased pulsation of the carotid artery when it is involved by dissection. Numbness, coldness, and weakness of the legs follow extension to the external iliac arteries. Shock may be present, however, frequently the blood pressure is normal or elevated, even though the patient appears to be in shock. There may be difference in the blood pressure between the 2 arms or 2 legs, or between the arms and legs. The pulse was absent in the right arm of Blackford's and Smith's patient.[3] Occasionally pulsating areas may be seen along the aorta or its branches. Roesler *et al.*[35] described a pulsation in the left interscapular area which rapidly shifted its center. The heart is usually enlarged due to the preëxisting hypertension. The supracardiac dulness may be increased. Hemorrhage into the mediastinum or pericardial cavity results in a widening of the area of cardiac dulness, while

hemorrhage into the pleural cavity gives the usual signs of pleural effusion. The latter is more frequently seen on the left side, since rupture through the adventitia is more common in the arch or descending aorta. A systolic murmur at the apex is common and Resnick and Keefer,[33] among others, have pointed out the significance of the diastolic murmur which sometimes appears at the aortic area. A pericardial friction rub may at times be heard[23] and was noted in one patient in the present series. Râles at the lung bases are common. Palpation of the carotid arteries when one has been partially occluded gives a difference in intensity of the pulse on the two sides. At times the pulsations on the involved side are increased, perhaps due to spontaneous periarterial sympathectomy such as described by Hamburger and Ferris.[15]

Rumbling or blowing murmurs have been heard along the course of the aorta. Infrequent tenderness to palpation over the aorta has been noted. Touhy et al.[39] recorded the instance of a pulsating tumor over the upper abdomen. A double ticking metallic sound over the upper abdominal aorta and synchronous with each pulsation was heard by Drs. R. H. Stephenson and H. C. Dorris in one patient in the present group. This sound, which was heard independently by these two observers, was interpreted as evidence of a dissecting aneurysm. This sound disappeared within a period of 12 hours and no explanation could be found when necropsy examination was performed.

Bizarre neurologic signs follow involvement of the intercostal and lumbar arteries which, as pointed out by Rogers,[36] furnish a blood supply to the spinal cord. This may result in loss of reflexes, paresthesias and, at times, transient motor paralysis. Occlusion of the mesenteric arteries may give abdominal tenderness and rigidity and has led to abdominal operation.[16] Noticeable coolness of one leg indicates a narrowing of the lumen of the iliac artery on that side, either by dissection or by reflex spasm. The femoral pulsation in such instances is diminished or absent. This has led to an operation for peripheral embolism.[6c]

Course. The course of the disease is usually short, although patients have been known to live for years and die of another disease.[13] Claiborne and Hollar[7] reported a case in which the patient lived for 55 days before dying from the results of an acute dissection. Kellogg and Heald[20] state that 80% die within a few days, while 20% have a chance of recovery. Shennan, as quoted by Peery,[31] reported 74 cases which recovered. Other observers report the mortality rate in the first few days to be as high as 95 to 98%. A slight fever frequently develops if the patient lives as long as 24 hours. The blood pressure, which is at first low or normal, may become greatly elevated. Signs of pleural effusion may appear. If hemorrhage has been extensive, pallor of the skin or mucous membranes will be evident. Reisinger[32] reported 1 case which showed a progressive anemia which reached values of 7 gm. of hemoglobin and 1.95 million red cells. The pain may subside partially or wholly, and all too often the patient's appearance, when seen at this stage, may belie the true grave condition. Nausea and vomiting

often recur and vague abdominal distress may be felt. Irregularities in the cardiac rhythm sometimes follow narrowing of the ostia of the coronary arteries. Anuria and hematuria are the sequelæ of involvement of the renal vessels. Buckley[5] recorded an instance of pain in the loin and hematuria which simulated renal colic. Abdominal pain may follow obliteration of the lumen of the mesenteric artery. Congestive heart failure is rarely seen, although this has been reported as a cause of death.[32] With recurrence of pain, or in the presence of hemorrhage, signs of shock may appear. After a period of a few hours to days, death may occur suddenly and without warning as rupture occurs into the pericardial cavity, mediastinum, lungs,[14] pleural cavity or rarely into the peritoneal cavity.

The electrocardiogram reveals no characteristic changes. Left ventricular preponderance resulting from previous hypertension is commonly seen. When the dissection involves the ostia of the coronary arteries, elevation of the ST segments and inversion of the T waves in one or more leads may be seen. Arrhythmias are occasionally seen, and 1 patient (Case 6) in the present series developed ventricular tachycardia and presumably died of ventricular fibrillation following constriction of the right coronary artery at its beginning by the dissection. One patient of McGeachy and Paullin[26] developed a left bundle branch block. Cardiac tamponade may cause elevation of the ST segments or inversion of the T waves in the standard leads. Glendy, Castleman and White[12] reported a case which showed T wave changes in leads 2 and 3 which were suggestive of posterior infarction and at autopsy there was narrowing of the right coronary orifice. Weiss[40b] reported 1 case with myocardial infarction resulting from involvement of the left coronary artery at its beginning. One patient in this series (Case 5) developed a complete occlusion of the right coronary artery at its origin as a result of a dissection around the ostium.

Roentgenologic Evidence. Wood, Pendergrass and Ostrium[43] reviewed the Roentgen ray changes in a number of cases and found that frequently a widening of the arch and proximal portion of the descending aorta was seen with a radiolucent area outside of the main shadow. It is in this area that a rupture through the adventitia so commonly occurs. Hirschboeck and Boman[18] reported a case with these distinctive Roentgen ray findings. The heart is usually enlarged and the supracardiac shadow is widened in those cases in which the ascending aorta is involved. The trachea and esophagus may be deviated by the enlarged aorta. Mediastinal and pleural effusion each give a characteristic picture. Coronary occlusion,[3] pulmonary embolism, cerebral hemorrhage, spontaneous mediastinal emphysema, cholelithiasis, nephrolithiasis, ruptured peptic ulcer,[10] acute pancreatitis, acute appendicitis,[30] and coarctation of the aorta must at times be considered in the differential diagnosis.

The following 3 cases, presented in detail, demonstrate some of the features of dissecting aneurysm.

Case Studies. CASE 6. A 46-year-old negro woman entered the hospital on October 8, 1939, complaining of cramping pain in the epigastrium and

vomiting. The patient had had attacks of nocturnal dyspnea, pedal edema, dyspnea on exertion, palpitation and infrequent syncope during a period of 9 months. She had noticed nocturia for several years. She had been fairly well about 1 month prior to admission when she developed some swelling of her feet and legs and moderate shortness of breath on exertion. She was placed on

Fig. 1.—(Case 6.) Marked enlargement of the left ventricle and dilatation of the aorta shown: *1*, in Roentgen ray; *2*, in gross specimen. Arrow points to characteristic radiolucent area outside of the main aortic shadow caused by the dissection. *A*, Organized clot in media which gave rise to radiolucent shadow on Roentgen ray; *B*, extension of dissection to the base of aorta so that the right coronary artery is constricted at its origin.
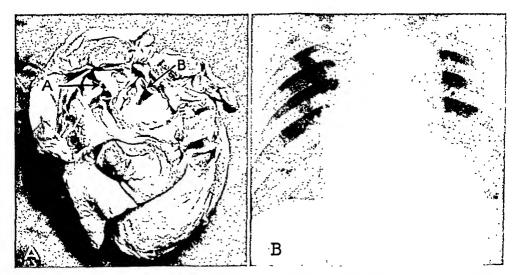
Fig. 2.—*A* (Case 8). A, intimal tear in the aorta; the separation of the edges is due to distortion; B, calcific stenosis of aortic valve. *B* (Case 2); enlarged left ventricle and tortuous aorta. The wide shadow indicates a mediastinal hemorrhage.

sedatives and digitalis in the Out-patient Department and improved somewhat. After 2 weeks she developed an intermittent cramping epigastric pain, which did not radiate and had no relation to meals. She had had intermittent attacks of epigastric pain above the umbilicus since a pregnancy in 1919, and these were associated with a small, reducible mass just above the umbilicus. On the evening of admission to the hospital, the patient developed a sharp, severe,

cramping pain in the epigastrium about 4 hours after supper. The pain was excruciating and caused her to double up. It was colicky in character and did not radiate. She vomited undigested food on 3 occasions. The emesis caused an accession of the pain.

Physical Examination. A well-developed and nourished woman, thrashing about in bed and complaining of severe pain in the epigastrium. Temperature was 96° F.; pulse, 86; respirations, 24. The blood pressure was 210/140 in each arm. The blood pressure in each leg was 270/160. The skin was cold and clammy. The heart was markedly enlarged to the left, the apex impulse being in the 6th interspace 12 cm. from the midsternal line. There was a soft systolic murmur at the apex. The second sound at the aortic area was accentuated. The liver was enlarged about 2 cm. beneath the costal margin. Auscultation
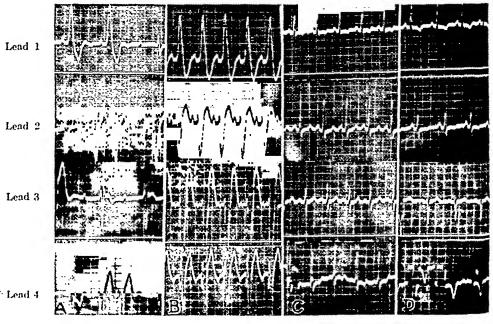
FIG. 3.—A (Case 6), Left bundle branch block, third degree heart block, frequent ventricular premature contractions, elevated ST-3 and depressed ST-4. At autopsy there was narrowing of the right coronary artery. B, Tracing 5 days later showing auricular tachycardia and left bundle branch block. C (Case 1), T waves inverted in leads 1 and 4 with low ST takeoff in leads 1, 2 and 4; left ventricular preponderance. D (Case 2), Slight sagging of ST segment in leads 1, 2 and 4; inverted T wave in leads 1, 2, and 4 and left ventricular preponderance.

of the abdominal aorta revealed a double, metallic, clicking sound, which was synchronous with each pulsation of the aorta. A small reducible hernia was present just above the umbilicus.

The pain subsided somewhat after a dose of morphine. The patient continued to complain of some abdominal distress, and would sit up in bed and rub her abdomen. She seemed to get some relief from pressure over the abdomen, and at times an enema brought remission of the pain. The abdomen was always soft and there was no localized tenderness. The patient had frequent spells of dyspnea, and at times showed Cheyne-Stokes respiration. The pulse was irregular and an electrocardiogram on the 2d day showed frequent ventricular extrasystoles with elevation of the ST segment in lead 3 and depression in lead 4F. On the 6th day the ventricular tachycardia had become constant (Fig. 3, A, B). Quinidine 0.3 gm. was given and following the 3d dose,

the patient complained of precordial pain. She had a slight convulsion and the heart sounds stopped. Occasional respiratory gasps were noticed for 5 or 6 minutes. The clinical diagnosis was: (1) coronary occlusion, and (2) dissecting aneurysm of the aorta.

Autopsy. A dissecting aneurysm of the aorta caused a narrowing of the ostium of the right coronary artery and the origin of the right innominate artery. The dissection extended to the origin of the right hypogastric artery. There was no tear in the intima. There was an organized clot in the media of the arch and descending portion of the aorta. Concentric myocardial hypertrophy and granular contraction of the kidneys were present. Twelve hundred cc. of amber fluid was removed from the left pleural cavity.

CASE 10. H. G., a 50-year-old white male, was admitted to the hospital complaining of severe pain in the epigastrium and right lumbar region. While walking home on the afternoon of admission, the patient was struck by a sudden sharp, severe pain in the epigastric region, which radiated to the right upper quadrant and to the right loin. The pain was intermittent and colicky in character. He was admitted to the hospital about 4 hours later and ½ gr. of morphine was necessary to secure relief from the pain. The blood pressure was 180/130 in the right arm and 130/100 in the left arm. The blood pressure in each leg was 200/150. The patient was sweating profusely and tossing about in bed with severe paroxysms of pain. The neck veins were distended. The apex impulse was felt in the 5th intercostal space in the anterior axillary line. There was a moderately loud systolic murmur at the apex. There was dulness to percussion with diminished breath sounds and spoken voice over the right lower lung posteriorly. No râles were heard. The right upper quadrant and right loin were tender to palpation. A reddish, mottled discoloration was noted in both lumbar regions and over the upper portion of both thighs. A Roentgen ray revealed some cardiac enlargement with an elongated and dilated aorta. A circular area of density was noted in the region of the lower end of the esophagus and a diffuse density was present throughout the mid-portion of the right lung posteriorly giving the appearance of pneumonia. An electrocardiogram taken on the 3d day revealed a low amplitude of the QRS complexes in the standard leads with flattened T waves in leads 1 and 2 and inverted T waves in lead 3. The temperature which was subnormal on admission rose to 100.4° F. on the 2d day and averaged about 99.2° F. during the succeeding days. The pulse ranged from 100 to 120. A thoracentesis of the right chest on one occasion revealed a thin, dark, red bloody fluid and on another occasion bright red blood. The patient continued to have attacks of pain in the right upper quadrant and right loin, and on the 6th day after onset, following severe pain in the right chest and epigastrium, suddenly developed shock and died.

Necropsy. A dissecting aneurysm involved the descending and abdominal aorta with a saccular dilatation just above and below the diaphragm. There was no intimal tear but two separate tubes. A rupture had occurred through the adventitia of the distal portion of the thoracic aorta. A large hematoma weighing 1300 gm. was situated between the parietal pleura and endothoracic fascia, and extended from the apex to the 8th-9th ribs. This was connected directly to the posterior mediastinum and pushed the lung anteriorly. The right lower lobe of the lung was atelectatic due to compression by the hematoma. Extensive hemorrhage was found in the posterior mediastinum and in the retroperitoneal space of the upper abdomen. Longitudinal wrinkling of the aorta was noted. The heart weighed 310 gm. There were multiple infarcts of both kidneys. There was moderate atheromatosis of the aorta, microscopic sections revealed a thickened intima, calcification of the media, round cell infiltration, cystic spaces and some thickening of the media.

CASE 12. W. A., a 66-year-old colored male, was admitted to the hospital complaining of substernal pain and shortness of breath. He had noticed some substernal pain on exertion for about 15 years and for about 1 year had felt breathless after exertion. Six days prior to admission following a walk of 2 miles he was seized with a sudden, severe, tearing, substernal pain which radiated backward between his shoulder blades and to both shoulders and

down both arms as far as the elbows. Soon there was severe pain around the umbilicus followed by nausea and vomiting. He became dyspneic and orthopneic. These symptoms persisted during the succeeding 6 days. On the 5th day a watery diarrhea was noted.

On admission the temperature was 99.2° F.; pulse, 100; respirations, 26. The blood pressure was 170/90 in the left arm and could not be obtained in the right arm. The retinal arterioles exhibited a moderate degree of arteriosclerosis. The radial and temporal arteries were sclerotic. The pulse could not be obtained in the right radial. The heart was moderately enlarged to the left and a loud pericardial friction was heard over the precordium, being most intense at the second left intercostal space adjacent to the sternum. A soft systolic murmur was heard at the apex and at the aortic area. The aortic second sound was accentuated. Frequent extrasystoles were noted. Signs of pleural effusion were present at the left lung base. The epigastrium was tender to palpation. The pulse was present in each femoral artery, however, a thrill was felt on palpation of the left femoral artery. A buzzing noise could be heard on auscultation over the artery.

The patient continued to complain of pain in the substernal and umbilical regions, and large doses of morphine were necessary to secure comfort. A venous pressure taken at the level of the posterior axillary line gave a value of 195 mm. of saline. The value for the circulation time was 33 seconds using calcium gluconate. The value for hemoglobin was 11.4 gm. with 4.6 million red cells and 17,700 white cells with 95% polymorphonuclear leukocytes and 3% lymphocytes. The urine specific gravity was 1.017 and there was 1+ albumin with 4 to 5 white blood cells per high-power field. The sedimentation rate was 39 mm. per hour by the Westergren method. The stool was light brown in color and gave a 4+ benzidine test for blood. The Kahn was negative. The value for the NPN was 23 and for blood amylase 69 mg. of glucose.

TABLE 1.—SUMMARY OF FINDINGS IN 12 CASES OF DISSECTING ANEURYSM

Case	Age	Symptoms	Signs	Duration	Pathologic findings
1. CM	42	Sharp retrosternal pain radiating to neck, back, rt. hip and leg. Weakness, numbness of rt. leg	B.P. not recordable in arms or rt. leg; 80/60 left leg. 2d: B.P. rt. arm 150/90; left leg 130/84. Anuria. Venous pr. 225 mm.	30 hrs.	Hemopericardium. Transverse tear in intima 3 cm. above aortic ring, dissection down to rt. common iliac. Occlusion of rt. renal art. Concentric myocard. hypertr.
2. CM	50	Severe knife-like pain in region of lumbar spine, dyspnea, substernal aching, nausea and vomiting	B.P. rt. 300/140. Left arm 204/110. Tracheal tug with deviation to left. Systolic murmur at aortic area. Dulness and diminished breath sounds over left chest.	12 hrs.	Dissection beginning at celiac axis and extending to arch of aorta, where a rupture through the adventitia occurred. Left hemothorax. Concentric myocard. hypertr. Medionecrosis cystica.
3. CF	45	Substernal pain radiating to back	B.P. rt.arm 120/110; left arm 224/124. To-and-fro murmur at apex and diastolic murmur at aortic area.	12 hrs.	Hemopericardium. Transverse tear in intima 2 cm. above aortic ring. Dissection of aorta to its bifurcation. Narrowing of opening of innom. art. Concentric myocard. hypertr.
4. CM	38	Hist. of congestive heart failure for 1 yr. Diagnosis of syphilitic aortic insufficiency. Died of uremia.	B.P. 200/0 both arms. To-and-fro murmur over whole precordium. Marked enlargement of heart. Liver enlarged 4 cm. Marked pitting edema of extremities.	5 days	Intimal tear 2 cm. above aortic ring, dissection extending to bifurcation of aorta. Syphilitic aortitis and valvulitis. Heart wt. 775 gm. Mural thrombi in rt. auricle. Multiple pulmon. infarcts. Contracted kidneys.
5. CF	45	Sharp epigastric pain radiating to angle of left scapula	B.P. 165/90. To-and-fro murmur at aortic area. Tenderness with muscle spasm in epigastrium and left upper quadrant.	10 hrs.	Dissection beginning in 1st few cm. of aorta and extending to level of inf. mesenteric. Occlusion of ostium of rt. coronary by dissection.

TABLE 1.—(*Continued.*)

Case	Age	Symptoms	Signs	Duration	Pathologic findings
6. CF	46	Cramping pain in epigastrium, nausea and vomiting. Hist. of congestive heart failure for 9 mos.	B.P. arms 210/140. Legs 270/160. Heart mod. enlarged. Systolic murmur at aortic area. Liver enlarged 2 fingers' breadth. Double, metallic, clicking sound over the abdominal aorta. Developed ventricular tachycardia.	7 days	Dissection of media without intimal tear, extending throughout the whole aorta, causing narrowing of rt. coronary ostium and the innom. art. Organized clot in the media. Concentric myocard. hypertr. Gran. contraction of kidneys. Left hemothorax.
7. WM	50	Severe substernal pain radiating to rt. shoulder. Syncope. Hist. of hypertension and treatment for syphilis.	B.P. rt. arm 90/70. Left arm 130/80; head and eyes deviated to right. Weakness of muscles of left side of face. Hyperactive reflexes on left. Ankle clonus and positive Babinski. Anesthesia of left side of body. Rt. carotid pulse weak.	13 hrs.	Intimal tear in region of innom. art. and dissection of arch, extending to descending aorta. Hemopericardium.
8. WM	40	Slight pain at base of neck, later severe precordial pain. Hist. of rheumatic ht. disease. Previous diagnosis of aortic stenosis and aortic insufficiency	B.P. 110/90 rt. Left 120/100. Ht. much enlarged to rt. and left. Systolic thrill over precord. most intense over aorticarea. Systolicmurmur over precord. transmitted up neck vessels. Systolic pulsation in rt. 2d and 3d intercostal spaces.	6 days	Intimal tear 2.5 cm. above aortic ring. Dissection extending throughout thoracic aorta. Hemopericardium. Eccentric myocard. hypertr. Heart wt. 650 gm. Calcific aortic stenosis.
9. CF	49	Aching pain in left hypochondrium. Symptoms of congestive failure for 1½ years. Hist. of hypertension.	B.P. 164/110. Heart markedly enlarged. Gallop rhythm. Systolic murmur at apex. Liver enlarged 5-6 cm. Marked pitting edema of extremities	56 days	Transverse tear in intima 3.5 cm. above aortic ring. Dissection limited to ascending aorta. Extended into pericardial sac, with hemopericardium. Concentric myocard. hypertr. Heart wt. 650 gm. Gran. contracted kidneys.
10. WM	50	Severe epigastric pain radiating to rt. upper quadrant and to rt. loin. Profuse sweating.	B.P. rt. 180/130, left 130/100, legs 200/150. Dulness to percussion and diminished breath sounds over right lower lobe of lung. Tenderness to palpation over rt. upper quadrant and rt. loin. Systolic murmur at apex.	6 days	Hematoma (1300 gm.) bet. endothoracic fascia and parietal pleura from apex to 9th rib on rt. side. Compression atelectasis of rt. lower lobe. Dissection of desc. and abd. aorta. No intimal tear; rupture through adventitia into post. mediastinum and retroperit. space just above diaphragm. Longitud. wrinkling of aorta. Mult. infarcts of kidney. Medionecrosis cystica.
11. CM	66	Sudden, severe, tearing, substernal pain with radiation between the shoulder blades and down arms to elbows, followed by periumbilical pain, nausea, vomiting, diarrhea, productive cough.	B.P. 170/90 left arm. B.P not recordable rt. arm. Orthopneic. Moist rales at lung base. Heart enlarged. Friction rub over precordium. Systolic murmur at apex. Occas. extrasystoles. Bruit and thrill over left femoral art.	8 days	Hemopericardium 500 cc. Heart wt. 590 gm. Intimal tear at origin of left subclavian art., retrograde dissection with rupture into pericardial sac. Dissection along innom., left subclavian, sup. mesenteric, rt. renal and both ext. iliacs. Medionecrosis cystica.
12. CM	35	Substernal pain followed 30 min. later by severe pain in the region of left hip. Faintness.	B.P. 138/100. Ht. enlarged. Systolic murmur at apex. Coldness of both legs. Absent pulse in left femoral art.	3¼ hrs.	Hemopericardium (500 cc.). Intimal tear near the innom. art. Dissection involving two-thirds of circumf. of aorta and extending to rt. ext. iliac art. Medionecrosis cystica.

The patient continued to complain of substernal and periumbilical pain. There was some cough, hiccough and nausea and vomiting. The sensorium became progressively cloudy and the patient died 2 days after admission.

Autopsy. Hemopericardium (500 cc.). The heart weighed 590 gm. There was an intimal tear in the aorta at the origin of the left subclavian artery. The dissection extended proximally and ruptured into the pericardium between the aorta and pulmonary artery. Distally it extended on to both external and internal iliac arteries. There was a dissection along the innominate, and left subclavian arteries. The dissection extended 4 cm. along the superior mesenteric artery and along the right renal artery as far as the hilum of the kidney.

Comment. The average age of the 12 patients was 45 with a range from 35 to 66. Ten of the 12 patients gave a history of previous cardiovascular symptoms. Eleven of the group either had hypertension on admission or gave a history of previous hypertension. The 12th patient had a calcareous stenosis of the aortic valve.

Pain was the initial symptom in 10 cases. This was felt first in the substernal region in 6 cases, in the epigastric region in 3 cases, and in the lumbar region in 1 case. There was no complaint of pain by the 2 remaining patients. Neurologic signs or symptoms were seen in 2 instances, 1 patient (Case 7) having been admitted with a hemiplegia. An interesting sign noted in 1 instance was a thrill and bruit over the left femoral artery (Case 11). The duration of the disease varied from $3\frac{1}{2}$ hours to $4\frac{1}{2}$ weeks. Six patients died within 2 days.

The leukocyte count ranged from 6250 to 28,850. In 2 instances the count was normal and in 8 instances it was above 12,000. The sedimentation rate was normal at the time of admission in 4 cases, elevated in 3 cases. Albumin was noted in the urine of 6 patients. Electrocardiograms were obtained on 6 patients. There were no constant changes, however, abnormal ST segments and abnormal T waves were present in one or more leads of each electrocardiogram. Left ventricular preponderance was present in 4 records. First degree heart block was seen in 2 instances. Frequent ventricular extrasystoles and subsequent ventricular tachycardia was observed in 1 patient (Case 6). Frequent ventricular premature contractions were noted in 1 instance (Case 11).

A Roentgen ray of the chest was taken in 8 cases. Marked cardiac enlargement was noted in 6 instances and moderate enlargement in 2 instances. There was a widening of the supracardiac shadow in 3 cases. The characteristic radiolucent shadow outside of the main aortic shadow was observed twice. A mediastinal effusion was evident in the film of 1 patient (Fig. 2 *B*). The film in Case 8 showed an extreme eccentric bulging of the cardiac shadow to the right. This was due to the aneurysmal sac which formed the apparent right border of the cardiac silhouette.

At autopsy a mild to moderate degree of atherosclerosis of the aorta was found in each case. Medionecrosis cystica of the aorta was demonstrated in 5 cases. Four patients gave a history of syphilis or a positive Wassermann reaction, and syphilitic aortitis was found in only 3 cases. An instance of syphilitic aortitis with aortic insufficiency complicated by dissecting aneurysm is presented. The site of the primary tear in

the intima was located in the first 3 cm. of the aorta in 6 cases. There was an intimal tear in the region of the origin of the innominate artery in 2 patients and in the region of the celiac axis in another (Case 2). No intimal tear could be found in the aorta of 2 patients (Cases 6 and 11).

The cause of death was hemorrhage into the pericardial cavity with subsequent tamponade in 7 cases. Hemorrhage into the left pleural cavity, uremia, ventricular fibrillation and coronary occlusion were other causes of death.

Summary. A study of dissecting aneurysm of the aorta is presented. An antemortem diagnosis was made in 10 of the 12 cases observed and confirmed on necropsy.

Isolated instances of dissecting aneurysm complicating calcareous aortic stenosis and syphilitic aortic insufficiency are presented. A new sign of this disease is described, consisting of a bruit and thrill over the femoral artery.

A history of a previous hypertension, or an elevation of the blood pressure at the time of admission, was noted in 11 of the 12 cases.

Tamponade was the cause of death in 7 cases. Hemorrhage into the pleural cavity, uremia, coronary occlusion and ventricular fibrillation were other causes of death.

REFERENCES

1. AGNOR, E. B.: J. Med. Assn. Georgia, 26, 108, 1937.
2. BAKER, L. A.: Med. Bull. Vet. Admin., 17, 170, 1940.
3. BLACKFORD, L. M., and SMITH, C.: J. Am. Med. Assn., 109, 262, 1937.
4. BOYD, L. J., and WERBLOW, S. C.: Ann. Int. Med., 11, 845, 1937.
5. BUCKLEY, T.: J. Urol., 44, 816, 1940.
6. Cabot Clinic Case: (a) 2811, New England J. Med., 226, 456, 1942; (b) 27302, Ibid., vol. 225, 1941; (c) Ibid.
7. CLAIBORNE, T. S., and HOLLAR, E. D.: Am. Heart J., 15, 358, 1938.
8. CROWELL, P. D.: J. Am. Med. Assn., 77, 2114, 1931.
9. ERDHEIM, J.: Virchow's Arch., 273, 454, 1929.
10. FINKELSTEIN, R., and JACOBI, M.: Ann. Int. Med., 13, 1991, 1940.
11. GARDNER, E., GAILBRAITH, A. J., and HARDWICK, S. W.: Lancet, 2, 1019, 1939.
12. GLENDY, R. E., CASTLEMAN, B., and WHITE, P. D.: Am. Heart J., 13, 129, 1937.
13. GOULEY, B. A., and ANDERSON, E.: Ann. Int. Med., 14, 978, 1940.
14. HADLEY, H. G.: Med. Rec., 154, 20, 1941.
15. HAMBURGER, M. J., and FERRIS, E. B., JR.: Am. Heart J., 16, 1, 1939.
16. HAMMAN, L., and APPERBY, F. L.: Internat. Clin., 4, 261, 1933.
17. HOLLAND, L., and BAYLEY, R. H.: Am. Heart J., 20, 223, 1940.
18. HIRSCHBOECK, F. J., and BOMAN, P. G.: Minnesota Med., 5, 724, 1922.
19. JESSIMAN, J. B.: Practitioner, 143, 643, 1939.
20. KELLOGG, F., and HEALD, A. H.: J. Am. Med. Assn., 100, 1157, 1937.
21. KENNEY, J. F.: Rhode Island Med. J., 22, 108, 1939.
22. LEARY, T., and WEISS, S.: Arch. Path., 29, 665, 1940.
23. LEVITT, A., LEVY, D., and COLE, J. L.: J. Lab. and Clin. Med., 26, 290, 1940.
24. LOWELL, W. H.: Connecticut Med. J., 4, 724, 1940.
25. MALLORY, T.: Cabot Clinic Case 25382, New England J. Med., 221, 471, 1939.
26. McGEACHY, T. E., and PAULLIN, J. E.: J. Am. Med. Assn., 108, 1690, 1937.
27. MIDDLETON, W. S.: Personal communication.
28. MORITZ, A. R.: Am. J. Path., 8, 717, 1932.
29. NIEHAUS, F. W., and WRIGHT, W. D.: J. Lab. and Clin. Med., 26, 1248, 1941.
30. NORRIS, J. C.: South. Med. J., 32, 475, 1939.
31. PEERY, T. M.: Am. Heart J., 12, 650, 1936.

32. Reisinger, J. A.:   Arch. Int. Med., 65, 1097, 1940.
33. Resnick, W. H., and Keefer, C. S.:   J. Am. Med. Assn., 85, 422, 1925.
34. Roberts, J. T.:   Am. Heart J., 18, 188, 1939.
35. Roesler, H., Gifford, G., and Betts, W.:   Am. Heart J., 13, 426, 1937.
36. Rogers, H.:   Am. Heart J., 18, 67, 1939.
37. Rottino, A.:   Arch. Path., 28, 1, 1939.
38. Samson, P. C.:   Ann. Int. Med., 5, 117, 1931.
39. Touhy, E. L., Boman, P. G., and Berdez, G. L.:   Am. Heart J., 22, 305, 1941.
40. Weiss, S.:   (a) Med. Clin. North America, 18, 117, 1935; (b) New England J. Med., 218, 512, 1938.
41. White, P. D.:   Ann. Int. Med., 11, 115, 1935.
42. Whitman, R. W., and Stein, H. B.:   J. Med. Res., 44, 579, 1924.
43. Wood, C., Pendergrass, E. P., and Ostrium, H. W.:   Am. J. Roentgenol., 28, 437, 1932.
44. Wood, H., and Agnor, E. B.:   Personal communication.

ARTERITIS IN RATS WITH EXPERIMENTAL RENAL HYPERTENSION*

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The spontaneous development of a specific inflammatory disease of the arteries of rats identical with or closely resembling periarteritis nodosa of man has been reported by Wilens and Sproul,[4] who found the lesion in 9.7% of 487 rats dying of natural causes.   The incidence in different age groups was as follows: under 500 days, 0%; 500 to 700 days, 3%; over 900 days, 15.7%.   They point out that this spontaneous disease was not found until late middle life and became more prevalent as age increased.

A lesion identical with the above mentioned was found to occur in a high per cent of young rats 6 months to 1 year of age, which had been subjected to certain experimental procedures to induce hypertension. It is the purpose of this communication to record these findings.

Experimental Procedure.   Thirty-seven albino rats which varied in age from 6 months to 1 year were studied at autopsy.   For the purpose of inducing hypertension these animals had been subjected to various operative procedures, no attempt being made to maintain aseptic technique.   A layer of cotton cloth was applied to the surface of both kidneys of 25 animals and to one kidney of 8 animals, according to the technique described by Grollman and Williams.[3]   A layer of collodion was applied to the surface of one kidney and a layer of cotton cloth to the opposite kidney in one animal.   One animal was subjected to the partial nephrectomy, according to the technique of Chanutin and Ferris,[1] followed by removal of the opposite kidney.   In a single animal a figure-of-eight silk suture was taken around one kidney and the opposite kidney removed.   In one animal a similar figure-of-eight suture was taken around one kidney and a layer of cotton cloth applied to the surface of the opposite kidney.

Postmortem examinations were performed ½ to 6 hours after death.   The majority of animals were found dead in their cages, although some were discovered in a moribund state and sacrificed.   The hearts were removed, after severing the great vessels at their proximal ends; the chambers were opened and all clots removed.   Their hearts were weighed to 0.1 gram and the per cent of

variation from the expected heart weight, as determined from a chart prepared by Donaldson,² recorded. Blocks of tissue for histologic study were fixed in Zenker's fluid with 10% acetic acid and stained with hematoxylin and eosin. The systolic blood pressure of these animals was determined weekly by the plethysmographic method described by Williams, Harrison and Grollman.⁵

Table 1 shows the type of operation, date of each operation, date of onset of the arterial hypertension, degree of hypertension and duration of the hypertension.

TABLE 1.—EXPERIMENTAL HYPERTENSION IN 39 RATS.

Rat No.	Date of first operation	Type of first operation*	Date of second operation	Type of second operation*	Date of onset of hypertension†	Date of death	Duration of hypertension, days	Minimal and maximal systolic B/P, mm. Hg.
1	8- 5-41	Cotton	10-23-41	Cotton	12- 1-41	1- 3-42	33	160–180
2	9- 1-41	"	10-23-41	"	12- 1-41	1- 4-42	34	160–195
3	11- 1-41	"	11-22-41	"	12-15-41	1- 6-42	22	155–190
4	11- 1-41	"	11-13-41	"	12-15-41	1- 7-42	23	160–220
5	7-30-41	"	8-20-41	"	10- 1-41	1- 8-42	99	165–185
6	10- 7-41	"	None	.	12- 1-41	1- 8-42	38	140–150
7	12-15-41	"	"	. .	12-30-41	1- 7-42	8	150–165
8	10- 7-41	Cotton Rt.	"	"	12- 1-41	1- 8-42	69	150–170
9	10- 1-41	" "	"	.	11- 1-41	1- 8-42	69	150–170
10	7-15-41	Cotton	10-25-41	Cotton	12- 1-41	1- 9-42	39	150–160
11	7- 5-41	"	8-18-41	"	1- 9-42	1-10-42	1	140–150
12	12-18-41	Cotton Rt.	11-14-41	"	1- 1-41	1- 9-42	8	150–155
13	11- 1-41	Cotton	11-14-41	"	12- 1-41	1- 9-42	39	150–200
14								
15	11- 1-41	"	11-17-41	"	12-15-41	1-11-42	27	150–170
16	7-15-41	"	8- 1-41	Rt. silk tie operation	10- 1-41	1-12-42	103	150–250
17	10- 1-41	"	10-13-41	Cotton	11-15-41	1-14-42	60	150–170
18	11-15-41	Cotton Rt.	None		. .	1-14-42	.	130–135
19	11-14-41	" "	"	.	12- 1-41	1-14-42	44	150–170
20	11- 1-41	Cotton	11-22-41	Cotton·	12-10-41	1-17-42	38	150–180
21	11- 1-41	"	11-14-41	"	12-10-41	1-16-42	37	150–190
22								
23	10-15-41	"	11- 1-41	"	12- 1-41	1-20-42	50	150–200
24	8- 1-41	"	8-18-41	"	10- 1-41	1-20-42	111	150–170
25	11- 1-41	"	11-22-41	"	12-15-41	1-22-42	38	150–160
26	7-15-41	"	8- 2-41	"	10- 1-41	1-26-42	ͬ17	150–190
27	11- 1-41	"	11-14-41	"	12-10-41	1-30-42	41	150–200
28	11- 1-41	"	11-15-41	"	11-20-41	1-31-42	42	150–180
29	12- 8-41	Cotton Rt.	None	.	1- 1-42	1-31-42	30	150–160
30	11- 1-41	Cotton	11-13-41	Cotton	12-20-41	2- 5-42	47	150–190
31	10-10-41	"	11- 1-41	"	12 1-41	3- 3-42	92	150–160
32	12-20-41	"	1-10-41	"	2- 1-42	3-13-42	40	150–200
33	1-20-42	"	1-31-41	"	2-20-42	3-18-42	26	150–180
34	8- 2-41	Silk tie operation	8-12-41	Right renectomy	10- 1-41	3-17-42	167	150–190
35	10- 1-41	Collodion, Rt.	11- 1-41	Cotton Rt.	1-30-42	3-23-42	52	150 190
36	4- 1-42	Partial nephrectomy	4-15-42	Left nephrectomy	5-15-42	6- 5-42	21	150 225
37	11-28-41	Cotton	12-15-41	Cotton		6- 5 42		120–140
38	11-28-41	"	12-15-41	"		6- 5-42		110–140
39	12-28-41	"	12-15-41	"		6- 5-42		110–130

* Description of various operations given under experimental procedure.
† Systolic blood pressure 140 or over.

Pathologic Observations. *Gross Description.* Concentric hypertrophy of the left ventricle was noted on gross examination of the hearts of 20 animals. No other macroscopic cardiac lesions were seen. Con-

gestion of the lungs was evident in 15 cases. Small areas of hemorrhage were seen in the subserosa of the terminal ilium and proximal portion of the colon in 2 rats. Moderate enlargement of the spleen was seen in 12 rats associated in each instance with evidence of marked infection of the kidneys. No remarkable gross lesions of the liver, pancreas, or adrenals was found. Perirenal abscess formation, associated with varying degrees of destruction of kidney tissue, was noted in 24 animals. This lesion was bilateral in 8 instances. All of the infected kidneys had had cotton cloth applied to their surfaces. These lesions varied from a minimal lesion involving the perirenal tissue to complete destruction of all kidney tissue. A thin layer of firm gray tissue, which seemed to be fibrous tissue, was noted surrounding the cotton in the rats which showed no evidence of secondary infection. No lesions of the ureters or bladder was observed. The genital organs of all animals appeared normal.

Inspection of the aorta of each rat revealed no gross changes. The mesenteric arteries of 11 animals showed striking gross abnormalities. In 5 instances in which the lesions were severe the normal delicate structure of the mesentery and its vessels was completely altered. The vessels stood out as thick tortuous nodular structures varying from 0.5 to 4 mm. in diameter. On cut section the nodular enlargements were found to consist of two types of lesions, one of which consisted of localized dilatations of the lumina of the vessels. Some of these aneurysmal dilatations were filled with what appeared to be postmortem clots. Others seemed to contain laminated thrombi. The second type of nodular enlargement consisted of firm grayish red tissue which seemed to cause marked narrowing of the lumina. In cases where the lesions were less severe the arteries showed segmented involvement by the above described process. Gross vascular lesions were found only in the mesenteric vessels. The ventricles of the brain of 1 animal was filled with freshly clotted blood and there was an area of hemorrhage 3 mm. in diameter in the tissue of the left frontal lobe of the brain of this animal.

Microscopic Findings. The most remarkable microscopic lesion noted was an inflammatory change involving many of the arteries of 15 rats. As in the spontaneously occurring disease described above, there was much individual variation in the appearance of these lesions. The changes were most marked in the medium-sized and small arteries. Some vessels exhibited an accumulation of lymphocytes, plasma cells, monocytes, neutrophils, and eosinophils in the adventitia associated with proliferation of the fibrous tissue of this layer. In some instances these changes involved diffusely the outer layer of the vessels; in others the changes were focal, and produced nodular lesions in the periphery of the vessel wall. What appeared to be more advanced lesions showed involvement of the entire wall by the above-mentioned inflammatory process, resulting in complete destruction of the normal architecture of the vessel and marked narrowing of the lumen. In some sections, dilated vessels, the walls of which were infiltrated by lymphocytes, plasma cells, monocytes, neutrophils, and eosinophils were seen.

Often these dilated vessels were filled with organizing thrombi. Foci of necrosis associated with the disposition of fibrin was seen in the walls of some vessels.

Many small arteries whose walls were involved by the above-described granulomatous-like process showed hyaline necrosis of the intima with thrombus formation in the lumen. Other vessels which seemed to exhibit evidence of healing showed distorted walls consisting of partially hyalinized connective tissue surrounding thrombosed lumina which appeared to be recanalized. Various stages of this process were noted in all animals. The above-described microscopic lesions were found most frequently in the mesentery, subserosa of the gastro-intestinal tract, periadrenal tissue, peripancreatic tissue, kidneys and spleen. Lesions were also noted in testes, myocardium, striated muscle, liver, subcutaneous tissue, lungs and urinary bladder wall. Striking lesions were seen in the uninfected kidneys of the 15 animals in which arteritis was found. These lesions were present both in kidneys which had and which had not been subjected to operative procedures. All stages of arteritis were demonstrated, involving small arteries and arterioles. Some glomeruli appeared necrotic, others appeared partially hyalinized and others showed complete fibrosis. Many tubules appeared dilated. There was a generalized increase in the interstitial fibrous tissue. A few wedge-shaped areas of scarring were noted in the cortices. No recent infarcts were seen. Evidences of changes in organs secondary to obstruction of blood supply were seen in the kidneys as described above, and in 2 instances in the intestinal tract, where marked congestion of the blood-vessels and diffuse necrosis of the wall was seen. In the myocardium small focal areas of scarring were noted associated with the inflammatory vascular change, but recent myocardial infarcts were not seen. No lesions of the veins were noted.

Sections from 8 animals displayed bilateral renal abscesses and sections from 16 showed unilateral renal abscesses. Histologically, their kidneys revealed areas of suppuration destroying varying amounts of kidney tissue. In some cases there was infection of the perirenal tissue with minimal involvement of kidney tissue. In others there was complete destruction of the renal tissue. Scattered throughout the areas of suppuration were masses of bacteria which morphologically resembled staphylococci. Smears of this pus showed Gram-positive cocci in clumps. Changes which did not seem to be related to the inflammatory disease were noted in small arteries and arterioles of many of the tissues of a large number of these animals. These abnormalities consisted of medial thickening secondary to smooth muscle hypertrophy, areas of hyalinization in the wall and hyperplasia of the cells of the intima, and were seen in vessels which did not show necrosis, cellular infiltration or perivascular fibrosis. To determine the relationship of the observed changes to the systolic blood pressure and the heart size, histologic sections were examined without any knowledge of which rats exhibited arterial hypertension. The degree of these changes in vessels which showed no evidence of inflammatory

TABLE 2.—RELATIONSHIP OF VASCULAR SCLEROTIC CHANGES TO SYSTOLIC BLOOD PRESSURE, HEART WEIGHT AND DURATION OF HYPERTENSION.

Degree of arteriolar and small artery sclerosis

Rat No.	Duration of hypertension (days)	Systolic B.P. (mm. Hg)	% change in heart weight	Myocardium	Subserosa	Muscularis	Submucosa	Liver	Spleen	Pancreas	Periadrenal tissue	Adrenal	Right kidney	Left kidney	Skeletal muscle	Subcutaneous tissue	Meninges	Brain	Arteritis

process were estimated and recorded in terms of $1+$ to $4+$. These findings are summarized and recorded along with the changes in heart size, the systolic blood pressure and the duration of arterial hypertension, when present, in Table 2.

Discussion. The two types of lesions, the inflammatory arterial lesion and the small artery and arteriolar sclerosis which have been observed will be considered separately. A conclusive analysis of the factors concerned in the pathogenesis of these inflammatory changes, which resemble the lesions described by Wilens and Sproul[4] as developing spontaneously in rats over 500 days of age and which also resemble periarteritis nodosa of man, is impossible from the available information, but the following observations suggest some factors which may be concerned in the evolution of these lesions: (1) In a group of 37 rats varying in age from 6 months to 1 year, which had been subjected to several procedures for the purpose of inducing arterial hypertension, this lesion was found in 15 rats. (2) Of these animals, 24 exhibited elevated systolic blood pressures and had a suppurative infection involving one or both kidneys which developed secondary to the application of a layer of cotton to the surface of the kidney. Arteritis was found in 12 (50%) of these 24 animals. (3) This same inflammatory lesion of the arteries was found in 3 rats of a group of 9 (33.3%), which showed arterial hypertension not associated with infection. (4) Only 2 animals which exhibited suppurative renal infection unassociated with arterial hypertension were studied. These animals showed no evidence of this arterial disease. (5) Two rats which had neither infection nor arterial hypertension were studied and no instance of arteritis was found. (6) The degree of the arteritis was much less marked in the animals which had arterial hypertension unassociated with infection as compared to that found in the rats with hypertension and a suppurative renal infection.

The above-described observations suggest that experimental renal hypertension alone or in combination with a suppurative infection of the kidneys played a part in the development of this inflammatory arterial lesion. Wilens and Sproul,[4] in discussing the etiology of the spontaneous arteritis of rats, mention the frequency of suppurative lesions in these animals, but state that similar suppurative lesions occurred with equal frequency in the absence of inflammatory arterial disease. They mention a possible relationship of this disease to the diet of the animals. The disease was found only once in a group of 75 rats receiving "a meat and vegetable diet," while it occurred in 46 out of 356 animals whose diet consisted largely or entirely of dried milk powder and ground wheat. There was no significant difference in the age of these animals or in the incidence of foci of suppurative infection in the two groups. The diet of the group of animals forming the basis of this report consisted of a commercial preparation containing protein 30%, carbohydrates 46%, fat 6%, bone meal 8%, and crude fiber 3%.

Wilson and Byrom,[6] in describing arterial lesions, found in rats in which sustained hypertension had been produced by partial occlusion
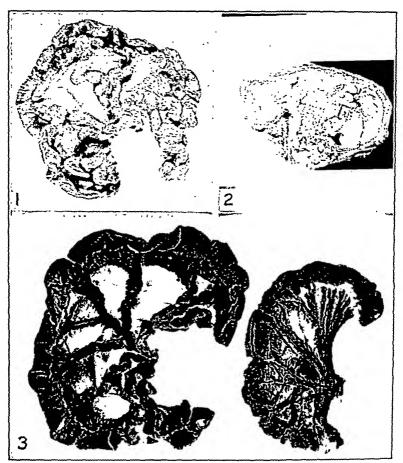
FIG. 1.—Gross appearance of the mesenteric arteries demonstrating a marked degree of arteritis.

FIG. 2.—Gross appearance of the cut surface of a kidney, showing extensive suppurative infection secondary to application of a layer of cotton to its surface.

FIG. 3.—Comparison of the appearance of the mesenteric vessels, exhibiting moderate degree of arteritis (on left of figure) with normal mesenteric arteries (on right of figure).

Legends for Illustrations on Opposite Page:

FIG. 4.—Arteritis of mesenteric artery with changes in the adventitia. Hematoxylin and eosin stain. (×70.)

FIG. 5.—Arteritis of mesenteric artery showing necrosis of and cellular exudate in adventitia and media. Hematoxylin and eosin stain. (×70.)

FIG. 6.—Portion of the wall of a mesenteric artery demonstrating arteritis associated with thrombosis. Hematoxylin and eosin stain. (×120.)

FIG. 7.—Arteritis of small arteries of testicle showing the primary and healing stages. Hematoxylin and eosin stain. (×120.)

FIG. 8.—Two small arteries of testicle exhibiting marked fibrosis of adventitia and medial necrosis. Hematoxylin and eosin stain. (×525.)
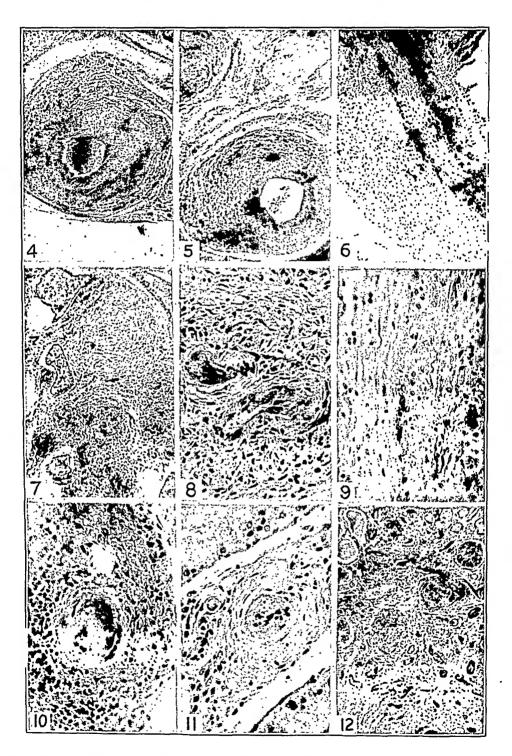
FIG. 9.—Organizing thrombus in a mesenteric artery. Hematoxylin and eosin stain. (×525.)

FIG. 10.—Necrosis of and cellular exudate in the wall of a small artery in periadrenal tissue. Hematoxylin and eosin stain. (×525.)

FIG. 11.—Small artery of testicle showing necrosis of media and marked fibrosis of the adventitia. Hematoxylin and eosin stain. (×525.)

FIG. 12.—Kidney showing arteritis of a small artery, necrosis of an arteriole, tubular dilatation, increase in interstitial fibrous tissue, glomerular tuft necrosis, and glomerular fibrosis and hyalinization. Hematoxylin and eosin stain. (×120.)

of one renal artery, point out that "the most severe lesions were found in the mesenteric arteries where gross changes resembling periarteritis nodosa were not uncommon." No further description of this lesion

is given. These workers state that all of their animals were under 500 days of age. In considering the pathogenesis of any vascular lesion found in rats with experimental hypertension, the fact that an inflammatory vascular disease which resembles the spontaneous arter-

itis occasionally found in this animal occurs frequently following procedures used to induce hypertension must be kept in mind.

Further investigation will be required to determine the exact relationship between this inflammatory panarteritis and the inflammatory arterial disease of man, periarteritis nodosa. Wilens and Sproul[4] point out that the spontaneously developing arteritis of the rat, which exhibits the same histologic changes as the arteritis found in our animals, demonstrates many features which makes it seem probable that it is closely related to periarteritis nodosa in man. These features include the anatomic changes, the distribution of the lesions, and the mode of onset and development of permanent residual deformities. The susceptibility of the medium-sized arteries is found in both diseases. The striking dissimilarities of the human and rat disease are as follows: The disease is rare in humans and it is one of the most common forms of systemic vascular disease of rats. The human disease occurs in all periods of life, while in the rat the lesion is found only in old animals.

It is hoped that continued investigation of the arteritis produced in rats may elucidate some of the factors concerned in the pathogenesis of inflammatory lesions of arteries.

The small artery and arteriolar changes found in these animals which did not seem to be related to the inflammatory arteritis will now be discussed. These consisted of medial hypertrophy, hyalinization of the walls and intimal hyperplasia unassociated with necrosis, infiltration of inflammatory cells and increase in fibrous tissue in the adventitia. These alterations were found in all of the animals which showed elevation of the systolic arterial pressure. A study of Table 2 shows that the severity of these arterial lesions is related to both the degree of arterial hypertension and the duration of the hypertension. Which of these factors is the most important is not obvious. It is also evident that these vascular changes in most instances are associated with cardiac hypertrophy.

These lesions tend to be more severe in the loose areolar connective tissues of the subserosa and submucosa of the gastro-intestinal tract, the periadrenal tissue, the peripancreatic tissue and the subcutaneous tissue. Also, as pointed out above, they seem to be related to the degree and duration of the hypertension. These findings suggest the possibility that the physical strain on the vessel walls due to stretching, secondary to the increased arterial tension, may be greater in this type of tissue than in the denser tissues of the body. The latter could conceivably offer more support to the vessel than the loose areolar tissue. The evaluation of the part played by this factor in the production of some of the vascular changes seen secondary to hypertension requires further study.

It is more difficult to interpret the lesions seen in the arterioles of the kidneys of animals with arteritis. These consisted of necrosis of their walls and infiltration by inflammatory cells. Whether these result from the increased arterial tension, whether they are a part of the picture of the inflammatory arteritis or whether they are a product

of the continued effect of the two processes is not obvious. Arteriolar necrosis was seen only in the kidneys of animals which also showed arteritis of medium-sized and small arteries.

Summary. 1. A form of arteritis similar to that described as occurring spontaneously in rats over 500 days of age has been found to occur in a high per cent of rats under 400 days of age, which had developed either arterial hypertension and a suppurative infection of one or both kidneys, or arterial hypertension unassociated with renal infection, following the application of a layer of cotton cloth to the surface of one or both kidneys.

2. The pathologic anatomy of this disease is described and the similarity of these lesions to the lesions of periarteritis nodosa of man is pointed out.

3. Other arterial changes which do not seem to be related to the inflammatory arterial disease are described and a possible factor in their pathogenesis is discussed.

REFERENCES

1. CHANUTIN, A., and FERRIS, E. F., JR.: Arch. Int. Med., 49, 767, 1932.
2. DONALDSON, H. H.: The Rat. Memoirs of Wistar Institute of Anatomy and Biology, No. 6, Philadelphia, 1924.
3. GROLLMAN, A., and WILLIAMS, J. R., JR.: AM. J. MED. SCI., 204, 73, 1942.
4. WILENS, S. L., and SPROUL, E. E.: Am. J. Path., 14, 201, 1938.
5. WILLIAMS, J. R., JR., HARRISON, T. R., and GROLLMAN, A.: J. Clin. Invest., 18, 373, 1939.
6. WILSON, C. and BYROM, F. B.: Lancet, 236, 136, 1939.

THE MANAGEMENT OF OBESITY WITH EMPHASIS ON APPETITE CONTROL

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DURING this investigation a survey was made of the existing methods of controlling obesity. The restriction of food intake is still the basic principle in all successful attempts at treatment. Dietary restriction over a long period of time is exceedingly difficult in most cases without the aid of some agent that depresses the appetite. No attempt has been made in this presentation to outline the various therapeutic theories. For data relative to these the reader is referred to the review articles on this subject.[1,2,7,9,11,14,19,20,22] However, cognizance has been taken of this work when applicable. For the most part, the cases presented herein were similarly treated as problems of exogenous

obesity. When other etiologic factors were apparent, an attempt was made to correct them.

A careful history and physical examination were obtained on all patients. Contributing organic or functional disturbances were sought. Such factors as psychic imbalance were noted, for just as anorexia nervosa has been found to occur in individuals with a compulsion neurosis, so also was bulemia present in individuals who were mentally harassed. Therefore in some cases, measures other than dietary restriction were necessary to obtain weight loss. On the basis of the history and physical examination, appropriate studies were carried out, namely: complete blood count; Volhard water-retention test; B.M.R.; blood cholesterol, lipoid phosphorus, sugar; glucose tolerance; quantitative urinary hormone assays; and Roentgen ray of the sella and long bones.

Treatment in the main consisted of appetite-control, correction of eating habits, exercise and dehydration; endocrine and psychotherapy when indicated.

Control of Appetite. Among the agents that are used in the control of appetite are dextrose, amphetamine sulphate, propadrine hydrochloride, digitalis and belladonna. Lesses and Myerson[13] were the first to show that amphetamine, which is an adrenergic drug, would depress the appetite. Subsequent reports[5,12,15,16,17] have confirmed this observation. The authors have also used amphetamine in the early cases treated.

Propadrine hydrochloride was employed by Hirsh.[10] The authors have also investigated this substance for its ability to control the desire for food and were able to confirm his results.

Recently Bram[3] has advocated the use of digitalis as an appetite-reducing agent. The rationale was the anorexia and nausea resulting from the effect of this drug. Greene[8] has employed belladonna alone, and in combination with sedatives in a series of 45 patients to control the appetite. Bram and Greene state that no gross evidence of toxic phenomena was observed.

Subsequently, amphetamine sulphate, a racemic mixture, was separated into two optically active isomers; one which was dextro-rotatory and the other lævulo-rotatory. These two substances were independently investigated for their appetite-inhibitory action. Previously with the racemic amphetamine, certain undesirable effects were encountered. These consisted of insomnia, irritability, "edginess," tenseness, and occasionally gastro-intestinal irritability. These exciting factors were found to predominate in l-amphetamine. On the other hand, the d-amphetamine was found to include most of the appetite-depressant activity. The dextro-rotatory benzedrine was initially given ½ hour before meals. Subsequently it was found that the administration 1 hour before meals gave the optimal effect. Later it was found advisable to ration the drug according to the hunger periods encountered during the day. The dosage of the drug was increased with the tolerance. The maximum dose employed was 30 mg. and the average dose was 15 mg. per day.

Ryder,[18] Gordon and Von Stanley,[6] have attempted to curtail excessive appetite by the administration of dextrose in the form of tablets or grape juice, *ad libitum*. In many cases this served to dull the desire for food.

Correction of Eating Habits. At the inception of treatment, the patient was given a list of foods which were to be avoided and another list of foods from which the daily menu could be selected. The patient was advised as to the caloric content of foods so that the common misconception, limitation of bulk meant limitation of caloric intake, could be dispelled. It was felt that if the patient could not understand the necessity for the caloric restriction, there would be no coöperation. The usual diet prescribed varied from 900 to 1300 calories, was high in protein, low in fat and carbohydrate. The use of bulky low-caloric food is of obvious advantage. The necessity of assuring adequate vitamin intake in the form of concentrates was stressed. For an excellent source of varied daily menus of this type, reference is made to Bridges.[4] The patient was also instructed to eliminate from the diet those substances which whet the appetite, especially alcoholic beverages and condiments. The avoidance of carbonated beverages because of their high-caloric value was explained. The necessity for correcting overeating by the formation of new eating habits was emphasized. Once this was accomplished, the individual was able to get along with less food, without pangs of hunger.

Exercise. Setting-up exercises have long been used in the reduction of obese individuals. This is a worthwhile procedure providing the increased appetite as a result of increased activity is controlled.

Dehydration. Diuretics have long been known and used in the forms of natural spring water containing various mineral salts. Hot mud, steam baths, cabinet baths, Russian and Turkish baths are popular even today. The chief objection to the latter form of dehydration is the fact that the craving for fluid and its satiation soon replenishes the body stores. The present armamentarium of the physician includes several diuretics such as ammonium chloride, pituitrin, mercurials, potassium salts, and other metallic salts. The authors have employed, in cases of fluid-retention, enteric-coated ammonium chloride in doses ranging from 45 to 120 gr. per day, and in a few cases mercurial diuretics in doses not exceeding 2 cc. per week intravenously. If these were used more often, the urines were checked more frequently. With the prolonged use of these two diuretics, calcium depletion was noted in some cases. It was important to have the patient under careful observation when any of these diuretics were given.

Endocrine Therapy. Endocrine therapy in suitably selected cases was of value. In the presence of a low B.M.R., high cholesterol and lipoid phosphorus, and clinical signs of hypothyroidism, desiccated thyroid extract was used. Furthermore, it was believed that the administration of this drug in obese individuals with apparently normal thyroid function, was often effective in reducing body weight.

The authors adhere to the view that certain glandular imbalances are manifested by a characteristic distribution of body fat. In the

hypopituitary individual, the adipose tissue was usually confined to the pelvic and mammary regions, upper arms and thighs. In the hypothyroid patient, the adiposity was generalized in distribution. In the hypogonadal type, the distribution of fat was mainly trochanteric. These constitute three of the more commonly encountered endocrinopathies in which obesity is a factor. The treatment of these cases will be presented in detail in a subsequent paper.

It was found important to instruct these patients not to tamper with the diets or to adopt starvation rations because they felt that the loss in weight was not sufficiently rapid. As far as control of appetite in the cases presented herein, three groups of individuals were encountered. These were arbitrarily classified as follows:

1. Those who were able to restrict their caloric intake without the aid of appetite depressants. (Usually girls in their late teens and recently married women.)

2. Individuals who desired to lose weight but were unable to control the appetite. (The majority of the patients treated.)

3. Those who were unable to consistently adhere to a diet despite appetite depressants. (Chiefly middle-aged women and inactive youngsters with voracious appetites.)

The majority of the patients were women. The amount of weight-reduction attempted in an individual was dependent not only on their ideal weight for their age and height, but also on their sense of well-being and resistance to infection. An individual may be 50 lbs. overweight and lose 25 lbs. without any untoward effects. However, further attempts to reduce body weight occasionally may be attended by asthenia, and increased susceptibility to infection.

Treatment. *As a result of these various considerations the following* plan of therapy was adopted. Most cases were primarily treated on the basis that reduction in appetite would produce a reduction in weight, incident to a lowered caloric intake. At the institution of treatment, the patient was given a diet of the type previously outlined and was also informed as to the total number of calories permitted in 1 day so that this amount could be rationed as desired. Thus individuals could resort to 4 or 5 small meals or 2 more substantial meals per day. The patient was advised to limit fluid and salt intake. This diet to the exclusion of other therapy was continued as long as there was a progressive weight loss and the patient coöperated. When no further reduction took place it was usually because adherence to the diet had become difficult. At this point whether it occurred immediately or after several weeks, amphetamine sulphate, preferably the dextrorotatory form was given. The patient was interrogated as to what time of day hunger was most acute and the drug was administered one hour prior to this. The average dose was 15 mg. daily. If this dose subsequently failed to control the hunger, an additional 5 mg. was given at the appropriate time. In most cases the following régime was found to be most efficacious: 5 mg. upon arising, 5 mg. at 11 A.M., and 5 mg. at 4 P.M. Therapy was maintained in this manner with suitable changes in dosage until there was an absence in weight reduction

for a period of 2 weeks. The daily dose even in the most resistant cases was not allowed to exceed 30 mg. Treatment was continued in a few individuals as long as 18 months without any untoward effects. However, the authors have held to the view that the drug should only be used as a temporary expedient to facilitate the formation of restricted eating habits. This period may vary from 2 weeks to 6 months. This was determined by the substitution of placebos administered in the same way at various intervals throughout treatment. If the weight loss continued on the placebo, the latter was utilized thereafter and subsequently eliminated entirely. If during any phase of the aforementioned period, weight loss failed to occur, and it was believed that the patient was adhering to the diet, it was necessary to resort to additional therapeutic agents. The next step was to administer a mild diuretic such as enteric-coated ammonium chloride in divided doses (45 to 120 gr. per day) as tolerated. Potassium chloride or other potassium salts could also be administered. These inhibit sodium ions thus limiting the retention of fluids by the tissues. Subsequently 2 cc. of Salyrgan-Theophylline were given intravenously at weekly intervals. Recently the action of the mercurial diuretics was found to be enhanced by the addition of 10 cc. of 20% Sodium Decholin. During this phase of the therapy, kidney function was routinely checked, although no instance of kidney damage was encountered in this group. Obstetrical pituitrin was also found effective in some cases. When the patient became refractory to this additional therapy and the authors were convinced that the patient was carrying out the prescribed treatment faithfully, thyroid extract was employed. The dose ranged from $\frac{1}{2}$ to 3 gr. daily.

After the initial rapid weight loss, many of the patients began to violate the diet or had the desire to do so. Since the eating habits vary from those of their families and friends, it was difficult for them to adhere to their diet. Subsequently it seemed more desirable to give them intervals of temporary respite from the vigorous therapy. This was best accomplished by following each 6-week period, with a 2-week interval in which the patient was cautioned merely to attempt to maintain the weight *status quo*. During this time no doctor was seen and no medication was used. This procedure accomplished several things: (1) It determined whether or not the patient had acquired new eating habits. (2) It gave the patient mental relief and relaxation which was not present under supervision. (3) The patient was more amenable and coöperative to further treatment. (4) It better assured the attending physician that the patient would continue the treatment for longer periods of time.

The authors do not believe in harassing an uncoöperative patient to lose weight, because the mental anguish produced does not warrant the end-result. In most instances this type of patient usually regains the lost weight with amazing rapidity after cessation of treatment.

Results. Approximately 300 unselected cases of obesity were treated for varying periods of time, ranging from 2 to 18 months. The following cases are illustrative of the various types of obesity: (1) Hypopituitary. (2) Simple exogenous. (3) Fluid retention.
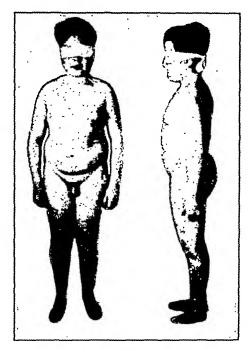
FIG. 1

FIG. 2
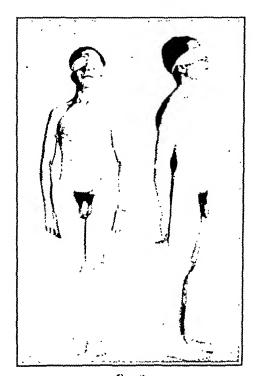
FIGS. 1 and 2.—Case 1. Hypopituitary obesity before treatment (Fig. 1) and 15½ months after start of therapy (Fig. 2). Note striking alteration in configuration and physiognomy.

Case Studies. CASE 1. Hypopituitary obesity. A 15½-year-old male, 55¾ inches tall, weighing 123 lbs. The blood pressure was 110/80 and the pulse was 70. At 5 years of age a severe case of measles was followed by an excessive gain in weight. The bodily configuration was characteristic of hypopituitarism. The appearance was that of a 12-year-old (Fig. 1). The B.M.R. was −9, the complete blood count and urinalysis were normal. There was 40% fluid retention. Because of an associated dwarfism, thyroid extract was given orally and pituitary growth extract by injection. A high-protein, subcaloric diet with adequate vitamin and mineral intake was prescribed. In the 14 months of therapy, there was a growth of 4½ inches and a weight loss of 12½ lbs. His weight reduction was much more significant than apparent from the actual figure as the patient was growing rapidly. The alteration in appearance from that of an obese youngster to that of a masculine youth was most striking (Fig. 2).

CASE 2. Exogenous obesity. A female, age 38, weighing 256¾ lbs., and 63½ inches tall. The blood pressure was 125/80 and the pulse was 80. The obesity began at the age of 7 with a sudden gain in weight which was progressive until the present. In one instance there was a loss of 78 lbs. in 6 months, as a result of dietary restriction. However, the weight was always regained following the cessation of the diet. There was occasional dyspnea upon exertion. The fat distribution was generalized, but was more marked over the abdomen. There was no water retention. The B.M.R. was +10. A 24-hour urinary excretion of prolan and estrogen were normal. The blood cholesterol was 205 mg. A 1000 calorie diet supplemented with vitamin concentrates was prescribed. Subsequently Dextrettes, amphetamine sulphate, 10 to 30 mg. daily, and thyroid, 1½ gr. daily were given according to the plan outlined previously. There was a steady loss of weight which totalled 86 lbs., in 9 months and was maintained for 2 months after cessation of therapy with a weight fluctuation of 5 lbs.

CASE 3. Fluid retention. A female age 53, weighing 385 lbs., and 60 inches tall. The blood pressure was 100/70 and the pulse was 88. The patient was thin until menarche at age 12, when there was a rapid gain of 50 lbs. There was a generalized fat distribution with a huge pendulous abdomen. Ankle edema was marked and folds of skin hung over the ankles. Complete blood count was normal. Urinalysis showed occasional hyaline casts with a trace of albumin; blood calcium was 10.5 mg.; blood cholesterol was 232 mg.; and the Volhard water retention test showed 95% retention. On the basis of the marked water retention, 90 gr. of enteric-coated ammonium chloride tablets were given in daily doses; an 885 calorie diet, high in protein, low in carbohydrate and fat with fluid restricted to 1000 cc. per day was prescribed. This was supplemented with vitamin concentrates. The urinary output was not increased and the patient complained of gastric upset. The ammonium chloride was discontinued and Salyrgan-Theophylline, 1 cc., was administered intravenously at weekly intervals with resultant diuresis. After 8 weeks of this therapy the diuretic effect was no longer observed. Decholin sodium, 20%, 10 cc., was then added to the Salyrgan-Theophylline, 1 cc. Marked diuresis ensued. This method of therapy was continued at weekly intervals for 8 months. There was a weight loss of 125 lbs.

The greatest weight loss encountered in this entire series was in this patient (Fig. 3). The least weight loss encountered was ½ lb. per week. The average weight loss for the entire group was 2 lbs. per week for the entire period of treatment.

In Table 1, 50 cases were presented which were representative of the group as a whole, and the weight loss was depicted at intervals of 1, 2, 4, 6 and 12 months according to the duration of treatment. In the entire group of 300 cases only one-third were still under treatment at the end of 6 months, while at the end of 1 year all but 10% had either dropped out or had been discharged.

The average weight loss during the 1st month of therapy for the entire group was 2½ lbs. per week. The average weight loss for the entire group for the 2d 4-week interval was 2.4 lbs. per week (range, 0.12 to 4.9 lbs.). The

average weight loss for the ensuing 8 weeks was 1.43 lbs. per week (range, 0.22 to 3 lbs.). At the end of 6 months of therapy the average weight loss was 1.2 lbs. per week (range, 0 to 3.1 lbs.). The average weight loss in those patients treated over a period of 1 year was 0.8 lb. per week (range, 0.17 to 1.6 lbs.).

TABLE 1.—WEIGHT LOSS ACCORDING TO DURATION OF TREATMENT

Case	Sex	Age (yrs.)	Hgt. (in.)	Initial (wgt., lbs.)	1 mo.	2 mos.	4 mos.	6 mos.	12 mos.
1	F	13	62½	159	144	136	134		
2	F	34	60	167½	167	166	150	126½	132½
3	F	16	64	165½	153½	146	144	155	147
4	F	25	62½	161¼	155	150½	143		
5	F	16	60	136¾	133	124	130		
6	F	35	71	235	226	231	20S	201	195
7	F	4S	61½	15S½	154½	153½	150½	155½	
S	M	12	56½	131	12S½	123½	124	124	
9	F	36	63	150	148	151	147½	141	126½
10	F	25	64	177	170	164	155	143	141
11	F	2S	62	213¾	205	202	200½	187½	18S
12	F	3S	63½	256½	23S½	221¼	194½	180½	173½
13	F	27	65	247	229	215	210	217	213½
14	F	29	63	257¼	243	223½	200	186	17S
15	F	33	64½	165¼	14S½	141	13S½		
16	F	2S	62	272½	263½	264			
17	F	23	65	177	162	156	160	165	16S
1S	F	49	61½	197	190	1S5½	167¼	155	145½
19	F	2S	62	1S9	1S3	173	154	14S½	
20	F	31	60½	136	124	119			
21	F	10	62½	147	13S½	129	121		
22	F	17	62½	170	15S	151			
23	F	15	62½	145	144½	143	131		
24	F	19	60	206½	209½	20S	205		
25	F	15	62½	161½	163½	147½			
26	F	45	61	217	213	195	17S	176	17S
27	F	34	61½	159½	145	139			
2S	F	12	55½	100½	90½	85½	8S½		
29	F	23	62½	1S1	170	161			
30	M	3S	64	203½	193½	1S4			
31	F	51	65	167	159	155½	148	142	
32	F	2S	59	132	122½	109	105½	112½	114
33	F	26	63	147	139¼	13S½	133½		
34	F	52	60	201	1S5½	174	16S		
35	F	47	62	1SS	1S0½	175½	170		
36	F	42	63	146½	140½	134			
37	F	51	61	167½	149½	145½	139		
3S	F	30	67½	179	167	15S½			
39	F	27	61	142½	134	127	120		
40	F	2S	61½	186	164	152			
41	F	30	62½	197½	1S1½	167½			
42	F	52	62	1S4	177	.	1SS½	162	
43	F	31	62½	211	190½	176	162		
44	F	27	61½	153	137½	126½			
45	M	29	66	19S	1S2				
46	F	30	61	1S2	170	163			
47	F	40	60	172½	156½	154½	147½		
4S	F	35	63½	163½	148	142	136		
49	F	42	62½	171	157	153			
50	F	30	61½	154	13S	127			

In those patients who were 100 to 150 lbs. overweight, the average weight loss for the 1st month of treatment was 3.4 lbs. per week, while the average weekly loss for the 1st 6 months of treatment was 2.9 lbs. per week, and for the 1st 12 months was 1.6 lbs. From the 6th to the 12th month the average weight loss was 0.6 lb. per week. In those patients who were 50 to 100 lbs. overweight, the average weekly loss for the 1st month was 3.1 lbs.; for the

1st 6 months, 1.6 lbs., and for the 1st year, 1 lb., while the average weekly loss from the 6th to the 12th month was 0.6 lb. In those patients who were 25 to 50 lbs. overweight, the average weekly loss for the 1st month was 2.2 lbs., for the 1st 6 months, 1.5 lbs., and for the 1st year, 0.71 lb. In this group it appears that there was no additional loss between the 6th and the 12th month. However, in those whom adequate loss was effected at the end of 6 months, treatment was withdrawn; while the few who had not lost sufficient amounts of weight were treated for the duration of the year, thus lowering the average weekly loss for the entire group (Fig. 4).
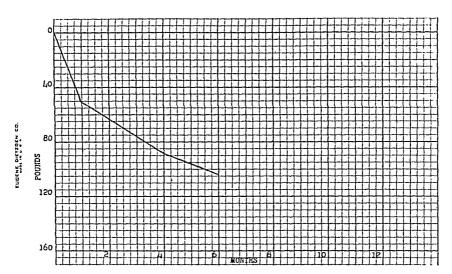
Fig. 3.—Weight loss in a case of water retention.
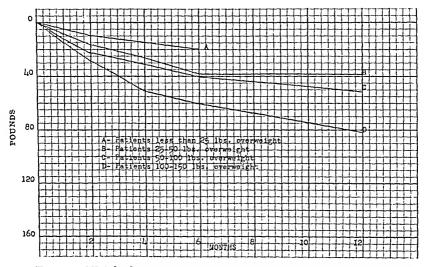
Fig. 4.—Weight loss in patients with various degrees of overweight.

In those patients who were not more than 25 lbs. overweight, the average weekly loss for the 1st month was 1.55 lbs., and for the 1st 6 months period was 0.6 lb. Treatment was not carried beyond the 6 months. From the foregoing it appeared that the average weekly weight loss was directly proportional to the degree of obesity. Instances of weight gain were offset by the subsequent weight losses in the same patients so that at the intervals noted, the average resulted in minimal losses as indicated in the ranges depicted above.

Discussion. As a result of 4 years of work in the treatment of obesity a plan of therapy has been evolved which the authors feel has proved most beneficial in effecting weight reduction in adipose individuals. It was obvious that to obtain adequate weight loss, food intake had to be restricted. This was best accomplished by controlling the appetite. In maintaining therapy sufficiently long to produce adequate reduction, it was important to prevent the patient from becoming discouraged. This was achieved by applying various therapeutic agents successively rather than all at one time. Thus each refractory period was met by utilizing an additional weight-reducing . factor.

There is currently no unanimity among investigators as to the specific etiologic factors in obesity. However, where a definite cause existed, appropriate selective therapy was administered.

Therapy was designed not only at reducing the weight of the patient without impairment of health, but also at attempting to create new eating habits. Obviously if the patient returned to old eating habits, the weight loss was rapidly regained. It was therefore important before commencing therapy to explain this fact to the patient. Therapeutists have not sufficiently stressed this point.

The follow-up of our patients showed that the majority of those in Group 1, the younger individuals who were more keenly interested in their appearance, maintained their weight loss long after treatment and supervision had been withdrawn. In Group 2 the incidence of those who maintained their weight loss was much smaller, while those in Group 3 for the most part did not warrant the effort involved.

In private practice, prolonged refractory periods which discourage the patient, could often be avoided by utilizing therapeutic agents successively as previously mentioned. The results obtained during the first months of therapy usually determined the future coöperation of the patient. The patient should be advised as to the regimen in general and as to the duration and mechanism, so that optimal coöperation may be obtained.

It has been noted that during the premenstruum there was a tendency to fluid retention and a refractoriness to weight loss despite rigid adherence to the dietary regimen, including restriction of fluid intake. This has been previously reported by Thorn, Nelson and Thorn[21] in a group of 50 normal subjects although they attributed this weight gain to an increased appetite and thirst during the premenstrual period. As the fluid intake in our cases was limited, this fluid retention was probably due to the increased estrogen elaborated during this phase of the cycle with a resultant retention of sodium chloride and fluid.

Some of the therapeutic suggestions outlined herein were utilized comparatively recently, so that it is possible that in subsequent cases on the basis of this plan, even better results may be obtained.

In an attempt to determine the relative toxicity of the dextroamphetamine, its ability to control the appetite, and its effect on drive, two of the authors (N. C. and A. S.) personally tested the drug.

One of us (N. C.) took 40 mg. over a period of 48 hours with complete abstinence from food, water, or sleep, although continuing his normal activities. No untoward effects were experienced and the loss of these three necessities caused no undue discomfort. Another one of us (A. S.) took 110 mg. of the drug over a period of 72 hours without any food, water, or sleep. Here again, efficiency and comfort were not disturbed for the first 48 hours. Subsequent to this, a number of toxic manifestations developed which cleared up following the cessation of the fast and the withdrawal of the drug. It must be remembered that no food or drink was taken at this time. The details of this experiment together with laboratory studies will be presented in a subsequent publication. Suffice it to say, the drug is non-toxic in doses up to 60–80 mg. over a period of 48 hours and has a remarkably exhilarating effect despite the absence of food, water, and sleep. In all the cases treated, only a few were unable to tolerate the drug, and in the majority of cases, adequate appetite control and increased drive was observed.

Appetite depressants such as previously mentioned were only of value in facilitating the formation of new eating habits. Once this was accomplished, the drug was withdrawn. Any attempt at weight reduction in obesity must accomplish this or therapy will ultimately prove of no avail.

The relative effects of the various appetite depressing agents utilized in this study, namely: dextro-amphetamine, racemic amphetamine, propadrine hydrochloride, and 1-amphetamine diminish in the order named. A few cases who could not tolerate dextro-amphetamine were able to utilize propadrine hydrochloride satisfactorily; in a few other cases the reverse was true. In 2 cases who were unable to tolerate dextro-amphetamine, the racemic compound was used without any untoward effect.

Summary. 1. Three hundred cases of obesity were treated by dietary restriction and appetite control.

2. Appetite was best controlled by dextro-amphetamine, although amphetamine and propadrine hydrochloride were found to be effective.

3. Treatment was aimed at correcting eating habits so that the patient would have less desire for the high caloric foods.

4. Various therapeutic agents (thyroid, ammonium chloride, Salyrgan-Theophylline, and Decholin Sodium) were added successively to eliminate each refractory period.

5. The average weight loss for the entire group for the therapy was 2 lbs. per week. The greatest weight loss was during the 1st month of therapy and averaged $2\frac{1}{2}$ lbs. per week.

6. As a result of this study, an effective plan of therapy in weight reduction was advanced.

REFERENCES

1. BARBORKA, C. J.: Med. Clin. of North America, January, 1937.

2. BAUER, J.: Arch. Int. Med., 67, 968, 1941.

3. BRAM, I.: Med. Rec., 153, 313, 1941.

4. BRIDGES, M. A.: Dietetics for the Clinician, Philadelphia, 4th ed, Lea & Febiger, 1941.

5. ERSNER, J. S.: Endocrinology, 27, 776, 1940.

6. GORDON, B., and VON STANLEY, E.: AM. J. MED. SCI., 175, 37, 1938.

7. GREENE, J. A.: Ann. Int. Med., 12, 1797, 1939.

8. GREENE, J. A.: J. Clin. and Lab. Med., 26, 477, 1940.

9. HAGEDORN, H. C., HALTEN, C., JOHANSEN: Arch. Int. Med., July 15, 1927.

10. HIRSH, L. S.: J. Med., 20, 80, 1939.

11. KNIPPING, H. W.: Med. Welt., p. 753, 1934.

12. KUNDSTADTER, R. H.: J. Pediat., 17, 490, 1940.

13. LESSES, M. F., and MYERSON, A.: New England Med. J., 218, 119, 1938.

14. MODERN, F. S., and JOHNSON, G. E.: Calif. and West. Med., 28, 660, 1928.

15. MYERSON, A.: New England Med. J., 221, 561, 1939.

16. ROSENBERG, P.: Med. World, 57, 656, 1939.

17. ROSENTHAL, C., and SOLOMON, H. A.: Endocrinology, 26, 807, 1940.

18. RYDER, W. H.: Med. Rec., 139, 663, 1934.

19. SELIGMAN, B.: Med. Rec., 146, 523, 1937.

20. SHORT, J. J., and JOHNSON, H. J.: J. Am. Med. Assn., 106, 1776, 1938.

21. THORN, G. U., NELSON, K. R., and THORN, D. N.: Endocrinology, 22, 155, 1938.

22. WEBER, S. J.: J. Missouri Med. Soc., 34, 158, 1937.

THE URINARY ELIMINATION OF PHENOLSULPHONEPHTHALEIN INJECTED INTO THE CEREBROSPINAL CAVITY IN SCHIZOPHRENIA AND GENERAL PARESIS*

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IT is the function of the barrier between blood and cerebrospinal fluid to regulate the exchanges and to maintain thereby a certain equilibrium between these two body fluids. Previous studies of the function of the barrier in both physiologic and pathologic conditions have relied essentially on functional tests which study the passage of

exogenous substances from blood into cerebrospinal fluid.[2] Yet, it is obvious that the absorption by the general circulation of substances present in the subarachnoid space affects the relationship between the constitution of blood and that of cerebrospinal fluid. This particular aspect of the function of the barrier has attracted the attention of research workers in the fields of neurology, neurosurgery and psychiatry.[2] This study was prompted by our general interest in the pathology of schizophrenia. It represents another attempt to use methods of study of the barrier function in research work in schizophrenia.

To begin with, we therefore selected 25 patients who showed distinct schizophrenic reactions. Information gathered from their life histories and the development of their illnesses added to the certainty of the diagnosis of schizophrenia of the type of Kraepelinian dementia præcox.

The obtained results made us feel the need for a control study in normal individuals. For obvious reasons such a study could not be undertaken. We, therefore, resorted to a distinctly organic condition, namely, general paresis (56 patients), for the purpose of comparing the behavior of the test, to be described presently, in a so-called functional condition—schizophrenia—with its behavior in an out and out organic condition—general paresis. Finally, in the light of the results obtained in this comparative study, the latter was supplemented by an investigation of our problem in 9 patients who approached normal individuals as nearly as possible: Two patients with reactive depression who at the time of the study were out of depression; 1 case of psychoneurosis, and 6 cases of psychopathic personality without psychosis.

TABLE 1.—RESULTS IN CASE 1 (M. B.) ILLUSTRATING PROCEDURE

'Phthalein injected into subarachnoid space	'Phthalein in urine	Elapsed time		'Phthalein in urine amount	'Phthalein in urine accumulated amount
Time	Time	Hours	Minutes	%	%
9:32 A.M.	10:03 A.M.	0	31	Trace	
	11:03 A.M.	1	31	3.0	3.0
	12:03 P.M.	2	31	8.0	11.0
	1:03	3	31	. .	11.0
	2:03	4	31	3.0	14.0
	3:03	5	31	5.0	19.0
	4:03	6	31	3 0	22.0
	5:03	7	31	3 0	25.0
	6:03	8	31	5 0	30 0
	7:03	9	31	0.7	30.7
	8:03	10	31	1.0	31.7
	9:03	11	31	1 5	33 2
	10:03	12	31	3.0	36.2
	11:03	13	31	3.0	39 2
	12:03 A.M.	14	31	3 0	42.2

Summary: a. 'Phthalein appeared in urine 31 minutes after the injection.
       b. 11% was eliminated after 2 hours, 31 minutes.
       c. The elimination still continued after 14 hours, 31 minutes, —3%.
       d. The total amount eliminated in 14 hours, 31 minutes was more than 42.4%.

Procedure. We used the test advised by Dandy. It consists in the subarachnoid injection of 0.006 gm. of phenolsulphonephthalein and study of its elimination through the urine. According to Dandy,[1] phenolsulphonephthalein introduced into the spinal subarachnoid space normally appears in the urine within 6 to 8 minutes; within 2 hours from 35 to 60% of the dye is eliminated.

Our procedure in the application of the test was as follows:

The patient was catheterized immediately before the lumbar puncture and the catheter was left in the urinary tract. The phenolsulphonephthalein injections (1 cc. of the standard solution—0.006 gm.) followed the removal of 2–3 cc. of spinal fluid. The urine was allowed to drip into recipients containing a few cc. of NaOH, so that the appearance of phenolsulphonephthalein in the urine could readily be observed. Beginning with the first appearance of the dye in the urine, the recipients were changed, as a rule hourly, and sometimes at longer intervals, for 6 to 17 hours. In each of these specimens of urine the amount of phenolsulphonephthalein was determined. The results obtained in each case were summarized under the following items: *a.* Time of appearance of phenolsulphonephthalein in the urine following its intraspinal injection. *b.* The amount of dye eliminated within 2 to 3 hours. *c.* The amount eliminated the last hour of observation. *d.* The total amount eliminated during the duration of the experiment.

Summary of Our Findings. *Schizophrenia—25 Patients.* (1) The time of appearance of phenolsulphonephthalein in the urine varied from 17 minutes to 1 hour and 47 minutes. (2) Within 3 to 4 hours the total amount of phenolsulphonephthalein excreted varied from 2% to 52%. (3) Within 6 to 7 hours the total amount of phenolsulphonephthalein excreted varied from 6% to 64%.

General Paresis—56 Patients. (1) The time of appearance of phenolsulphonephthalein in the urine varied from 6 minutes to 3 hours and 21 minutes. (2) During 3 hours the total excretion of phenolsulphonephthalein varied from trace to 78%. (3) During 6 hours the total excretion varied from trace to 79%.

Control Studies—Non-psychotic Patients—9 Cases. Two patients recovered from reactive depression. One psychoneurotic and 6 psychopathic personalities without psychosis. (1) The time of appearance of phenolsulphonephthalein in the urine varied from 6 minutes to 2 hours and 3 minutes. (2) During 3 hours the total excretion of phenolsulphonephthalein varied from 3% to 16%. (3) During 6 hours the total excretion of phenolsulphonephthalein varied from 14% to 70%.

Discussion. Our findings deviate markedly from those which Dandy reported as normal values. The time of appearance of the dye in the urine is considerably delayed in most cases. The total elimination of the dye during 3 hours is distinctly below the normal level in the bulk of cases. In evaluating the data of this study, the question arises whether or not they might be at least partly affected by the impairment of the kidney elimination of phenolsulphonephthalein. While it is to be regretted that the phenolsulphonephthalein test of the renal function was not done in each of our patients, there was, however, no suggestion in any of them of cardiovascular or kidney involvement, either in the clinical picture or in the urine examination. The phenolsulphonephthalein test for kidney function was, however, carried out in 12 patients; in all of them the urine elimination was well within

normal limits. Granting, that our data were not affected by any cardio-vascular or kidney malfunction, as appears to be the case, they should be attributed to slow return of the dye from the cerebrospinal cavity into the general circulation. It should be noted that the delay in the phenolsulphonephthalein excretion in our schizophrenic patients was similar and more marked than the delayed excretion in our paretic patients.

Similarly, Weston[4] in injecting phenolsulphonephthalein into the lumbar spinal cavity in dementia præcox patients, noticed a consider-able delay in the appearance of the dye in the urine. It is interesting to note that the delay was longer than in paretic patients. According to Mehrtens and West,[3] a marked delay in the urinary elimination of phenolsulphonephthalein from the subarachnoid space is a significant indication of an organic disease of the central nervous system in cases in which the cerebrospinal fluid findings are not contributory.

While these bibliographic data offer support for our findings in schizophrenic and paretic patients and also a fair background for evaluating them in favor of the concept that schizophrenia is an organic disease, we are not prepared to accept it as an established fact: first, that the absorption of phenolsulphonephthalein from the subarachnoid space into the general circulation is markedly delayed in schizophrenic patients and second, that the delayed elimination is indicative of organic involvement of the central nervous system. Our doubts are strongly suggested by our findings in the 9 non-psychotic patients. The delayed excretion is just as pronounced and in the first 3 hours even more marked than in the schizophrenic and paretic patients. Control studies in a fair number of normals are needed before one would be justified to use Dandy's findings as criteria of normality. Until well-established normal standards are available, the finding of this study should be regarded as factual material, as yet not ready for an adequate evaluation.

REFERENCES

1. DANDY, W. E.:   J. Am. Med. Assn., **61**, 2216, 1913.
2. KATZENELBOGEN, S.:   The Cerebrospinal Fluid and Its Relation to Blood, Baltimore, The Johns Hopkins Press, 1935.
3. MEHRTENS, H. G., and WEST, H. F.:   Arch. Int. Med., **20**, 575, 1917.
4. WESTON, P. G.:   Arch. Neurol. Psych., **5**, 58, 1921.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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THE CONSTITUTIONAL ASPECTS OF PEPTIC ULCER*

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A. Introduction. The concept of constitution has developed synchronously with man's increasing knowledge of heredity and environment. An excellent historical review of the evolution of the concept of constitution (hand-in-hand with the age-old controversy of heredity *versus* environment) can be found in a discussion by Tucker and Lessa.[119,120] As in every controversy, the pendulum ultimately comes to a halt at some point between the extremes of its former excursions; thus, the following definition can be made: constitution is the complete biologic cross-section of an individual at any one moment in his life, embracing the fixed terrain of his hereditary endowment on which is interplayed the product of environmental stress and his reacting tissues.[29,30,35,44,92,101,108,119,120] Involved, therefore, are an individual's morphology, physiologic equipment, racial background, age, sex, psychologic makeup, the complex interplay of the autonomic nervous system, endocrine system, and neurohumoral mechanisms, tissue reactivity to both physiologic and psychologic conditions, immunologic response and capacity, the results of environmental conditioning up to the moment of analysis, local tissue inferiority—all these factors—some fixed, some fluctuating with the impingement of environment—which, when integrated at any one moment in an organism's life, combine to form his constitution.[4,28,30,85,92,102,120]

When the interplay of these constitutional components makes for a diseased condition, such a constitutional orientation is termed diathesis.[4,17,29,59]

The scope of this paper is to review the predisposing terrain of gastric and duodenal ulcer. We do not plan to discuss the exciting etiologic factors except as they are related in a general way to the ulcer terrain. We shall present evidence that an "ulcer type" exists; analyze the ulcer constitution in its various panels; and show the etiologic significance of this terrain.

Certain conditions that on occasion are associated with peptic ulcer, or which are too infrequent to enhance our knowledge in the direction

of this paper, will be discussed very briefly or not at all. These include renal disease, hepatic disease, prostatic disease, intracranial lesions, sites of heterotopic gastric tissue, appendicitis, cholecystitis, pancreatitis, carcinoma of the gall bladder, Lane's kink, uremia, tuberculosis, syphilis, arteriosclerotic processes of the gastro-duodenal vessels and their sequelæ, malnutrition, the avitaminoses, sepsis, lead poisoning, cardiovascular disease, and external trauma.[51,57,73,98]

B. **Evidence for the Existence of an Ulcer Type.** 1. *Homogeneity of Constitutional Characteristics.* Older clinicians were famous for their "snap" diagnoses of certain diseases. Particularly susceptible to this type of diagnostic acumen are gastric and duodenal ulcer; for patients with these diseases have certain characteristics of personality, morphology, and physiologic activity in common. Ulcer is selective. Draper says "Many human beings pass through similar environmental influences without evident damage but peptic ulcer is a case of selective environmental action on favorable constitutional terrain."[29] Hurst,[65] Crohn,[21] Miller,[36] and other authorities[6,32,121] agree with this.

The study of man and his division into constitutional types was given impetus by the pioneer and fundamental work of Stiller, von Bergmann, Di Giovanni, Pende, Eppinger, Hess and others. Detailed anthropometric, psychoanalytic, and physiologic studies have been added to their efforts and applied in particular to the ulcer individual. A constancy of constitutional characteristics has been found. In fact, Hartman states "When one learns to recognize the type of ulcer bearing patient, one can predict that an ulcer is present almost without other aids."[50] Moynihan says he can diagnose an ulcer by correspondence, so pathognomonic is the psychologic panel.[50a]

Section C is devoted to the detail of the peptic ulcer constitutional panels. •Work presenting evidence both *pro* and *con* is given there, but the bulk of the work indisputably shows the tendency to homogeneity of the constitutional characteristics of gastric and duodenal ulcer patients— a fertile terrain for the seed of ulcer.

2. *Heredofamilial Tendency of Ulcer.* The familial tendency of ulcer with its underlying genetic implications is well accepted. Many interesting familial examples have been given.[21,45a,49,54,78,96] Statistical data is also prevalent[6,7,24,36,53,96,110,111,114] from which we summarize the following findings: (a) Families of peptic ulcer patients have a significantly greater incidence of peptic ulcer than families of normal people.[6,7] (b) The families of every series of ulcer patients show a high percentage with a history of some disease of the upper digestive tract.[21,32,36,110] The positive effect of the incidence of some form of stomach ailment in the grandparent on the incidence of ulcer in the F–2 generation is shown by Bauer.[6] (c) A striking series is presented by Willcox[124] in which he obtained a family history of ulcer in 35% and of dyspepsia in an additional 40% of 40 soldiers with peptic ulcer evacuated from France in 1940 in contrast to 4% and 2% respectively among soldiers with no digestive disorders. The distinguishing feature of this series is the fact that it contains people exposed to a practically identical environment.

Broader aspects have been investigated in this direction where an entire diathetic ensemble was apparent including the dominance of a morphologic type, general heredofamilial gastro-intestinal weakness, sexual preponderance in this latter respect and in diseases in the zone of the vagus nerve in the masculine direction, and catabolic disease susceptibility.[32,64,118]

The specific genetic mechanics have been suggested by some authors

but the problem is far from clear.   Dauwe[24] reports that ulcer is inherited from the mother, but Riecker[96] finds this an inconspicuous phenomenon in his series.   Aschner[32b] concluded that the gene for stomach inferiority is recessive and not sex-linked but Draper and Touraine[32] counter by saying that it is difficult to conceive of a specific gene weakness as being responsible for so complicated a disturbance of the vegetative nervous system as that which results in gastro-intestinal lesions.   They do not accept the condition as a recessive Mendelian phenomenon in view of the variability of external influences that may determine its expression.   For the present, the genetic mechanism has not as yet been specifically determined for this ulcer diathesis, but the linkage of many characteristics—morphologic, physiologic and psychologic—is involved.

Some authors disagree with the heredofamilial influence but not with its existence.[54,110]   They suggest the effect of hereditary habits and conditioned status that a family carries with it for generations and imposes on its siblings as being the important factor rather than the heredofamilial one.   It is these that make for the lack of absolutism in the field of constitutional terrain but it is Willcox's[124] series and other similar bits of evidence that show the effect of an inherited diathesis.

3. *Age Incidence.*   Statistical analyses and grouping of ulcer patients have shown that it is largely a disease of younger rather than older patients.[13,56,85]   To Morrison and Feldman,[85] this suggests an endocrinologic and nervous system background.   It is remotely possible to interpret this as a genetic phenomenon akin to delayed dominance.   It is, however, very difficult to exclude accumulative psychic trauma which is prone to play a large rôle in these age groups.   Highman's series[56] showed peptic ulcer very rare before puberty, a period of minimal psychic trauma.   Therefore, no very conclusive evidence can be gleaned from the age incidence of peptic ulcer as to the existence of the ulcer constitution. ·

4. *Sex Incidence.*   Many statistical surveys as to sex incidence in peptic ulcer have been made and variable results obtained.   There are two reasons for this: First, peptic ulcer was formerly considered a discrete entity *per se* but more recent work has indicated that the components of peptic ulcer, gastric ulcer and duodenal ulcer, are distinct *disease* entities in themselves.[15,32,36,59,66,80,108]   Some authors issued statistical reports without regard for the ulcer site; others have had regard for the site when they made their surveys.   Secondly, duodenal ulcer occurs 4 to 10 times as often clinically as gastric ulcer[36,80] and therefore statistics based on peptic ulcer distribution in the sexes without regard to anatomic site were overwhelmingly colored by the correlation between duodenal ulcer and sex.   It obviously makes no difference if the incidence of duodenal and gastric ulcer in the sexes were identical.

But they are not identical.   This report is based on those records in which a distinction was drawn between gastric ulcer and duodenal ulcer.   On the whole, duodenal ulcer occurs 4 to 5 times as frequently in men as in women.[56,81,110]   Gastric ulcer on the average occurs about twice as often in men as in women.[56,99,109]

Crile interprets sex predominance of a disease incidence as an "application of the genetic principle that the differences between the sexes are deeply rooted constitutional differences of psyche and soma."[20]   The genetic mechanism involved here is probably sex-linkage, where certain characteristics are borne in the unmasked "X" chromosome of the male that are in most instances masked by the occurrence of dominant genes in the other "X" chromosome of the female.   Presumably, then, *certain*

predisposing characteristics that make for duodenal or gastric ulcer are sex-linked and this is more quantitative in the case of duodenal ulcer. Certainly more exact statistical studies are in order in this direction with the proper respect paid to the site of the ulcer and the subsequent division of the group into gastric or duodenal.

5. *Racial Selectivity.* Most writers agree that peptic ulcer shows a unique selectivity in race. Peptic ulcer is more common among energetic racial types.[91] Several series in geographic areas where both native negro and white population lived found the pure negro and lesser pigmented races practically immune to the disease whereas the white race alone was susceptible.[2,21a,37,56,102,121]

It is difficult to evaluate the situation. Environment, such as climate and many other factors, plays a rôle. But the attitude of the natives studied as well as that of a group of Chinese[2a] was that of stoicism and relative apathy. There was not the driving tenseness and ambition of western civilization. Civilization is, to a certain degree, the expression of the nature and constitutional background of the peoples from whom it springs—and in this way, racial selectivity of ulcer points to the restless, striving, taut psychologic panel of the white man.

The fate of the American negro has an interesting bearing on the question just discussed. Upham[121] dealing with 200 American negroes who were living in the worst economic and nutritional conditions and whose mouths were full of focal infection had the inconsequential incidence of only 1 case of ulcer. On the other hand, Steigmann[112] disclaims that the negro is immune to peptic ulcer because of his absence of psychogenic stimulation, and presents a statistical review of peptic ulcer in negroes from Cook County Hospital to prove his point. An investigation of the socio-economic factors indicate the basis for psychic stimuli, anxiety, and so forth, and no doubt, these did not fall on barren soil.

Summarizing this aspect, just as ulcer is more common in the tense, striving, ambitious, high-strung individual than in the phlegmatic, apathetic person, so races whose psychologic makeup is of the latter type and whose civilization has its roots in such soil and is expressive of it and consists therefore of minimal psychic traumatic content, will be less prone to peptic ulcer. The white race exemplifies the converse. The mechanisms involved will be discussed under Section D. When the races whose psychologic panel is of the more passive variety are subjected to a life rich in psychogenic traumatic content they continue at first with a minimal reaction to their new environment but soon the neurogenic and psychogenic factors take hold, as illustrated by Steigmann's series.[112]

6. *Seasonal Fluctuation.* With almost mathematical regularity, peptic ulcer symptoms have been noted to recur in spring and fall. It has likewise been observed that these symptoms are generally more protracted and not so quickly influenced by treatment in the spring.[54] This phenomenon of variability might well be correlated with Wade H. Brown's concept of constitutional variation.[14,54]

7. *Recurrence and Multiplicity.* If a person has the constitutional orientation that predisposes to ulcer formation, we should expect peptic ulcers to have the characteristics of multiplicity and recurrence. Notation of the recurrence of ulcer has been made by Crohn,[21] Miller,[36] Hurst,[65] and others.[2,45,69,73] Friedenwald[45] and Hurst[65] recognize the importance of the recurrence of ulcer clinically in regard to prognosis, treatment and prophylaxis. Eliason[38] has said that the surgeon can remove an ulcer but cannot prevent its recurrence at another site if the patient is constitutionally predisposed to ulcer formation.

A statistical series on ulcer multiplicity made at Bellevue Hospital, the authors[117] found 29% of gastric ulcers multiple, and 50% of duodenal ulcers multiple.

8. *Experimental Ulcer and Psychosomatic Studies.* Experimental ulcer and psychosomatic studies are valuable in affording a link in explaining the mechanics by which a predisposing constitution can develop ulcer. The largest amount of work has been done in the direction of neurosomatic and psychosomatic experimentation.[22,48,53,58,70,90,130] Their results have contributed the following: (*a*) Neural pathways existing as an anatomic bridge between psychic centers and soma. (*b*) The gastric phenomena, such as hyperchlorhydria, hypermotility, and hypertonicity, which are shown by most peptic ulcer patients, can be produced by stimulation of the neurovegetative center in the diencephalon—a center easily affected by psychic trauma.[12,22,55,75] (*c*) The peptic ulcer lesion is limited to about 4 inches of the lesser curvature of the stomach and the first inch of the duodenum, because this region is richest in vegetative nerve supply.[102,105] It is these two regions that are subject to the most quantitative, neurogenic "blitzkrieg" which is especially severe in patients constituted of the psychologic type as our ulcer patient (*cf.* C. 2 below). (*d*) Wolf and Wolff[130] observing the stomach through a fistula have seen the local gastric manifestations and the actual production of an ulcer in a human, initiated through psychogenic stimulation.

Having suggested the mechanics and established the pathways,[1,27] an inherent diathesis explains why, under almost if not exactly identical environmental stimuli, some develop ulcers while others remain free. Diamond,[25] Held,[53] Hartman,[50] Cushing[22] and others attribute the ulcer-effect of extrinsic secondary causes as due to a fertile terrain, in which dysharmony, instability and unusual reactivity of the vegetative nervous system, attuned vagotonically, and impinging along grooved neural pathways to a postulated diencephalic parasympathetic center, lay the groundwork.

C. The Ulcer Terrain. By this complex factor, terrain, is meant the fertile soil on which the exciting causes of ulcer take root. Observations in this direction must be on pre-ulcer patients or on ulcer patients in which case attention is paid to those characteristics which are immutable and independent of the ulcer disease process. The question is simply: *Is a predisposing characteristic observed, or one resulting from the disease process?*

The changed nutritional state during the active phase of the disease might very well be reflected in morphologic changes. The presence of annoying symptoms, pain, inadequate rest can distort the psychologic panel.[85] The physiologic panel, when the measurements are made in the presence of an active ulcer, may display reflex phenomena, spasm in the gastro-intestinal tract, changes in acidity, etc., rather than the state of intestinal conditions which preceded and predisposed to active ulceration.

Feigenbaum and Howat criticize the entire physiognomic diagnosis of disease by saying that the disease itself may be responsible for morphologic changes and that these are manifestations of the disease.[43] Stenbuck[113] admits that the facies of ulcer patients changes strikingly with the state of ulcer development, nourishment and so forth. Rivers[97] objects to the anatomic pattern as being too fixed to explain so psychophysiologic and dynamic a problem as peptic ulcer.

Rivers' objection can be overcome by completing the constitutional pattern of peptic ulcer patients, which in itself includes psychophysiologic processes as well as morphologic. Draper uses chiefly anthropometric

indices and measurements which are fixed and immutable and independent of the ulcer disease. He qualifies these measurements which might be influenced by the disease process. For example,[26,29] he establishes the value of the ponderal index and significant low weight as part of the anatomic panel of the ulcer diathesis by calculating these on the basis of top weight, i. e., before symptoms ensued or after cure.

No observers have objected to the psychologic panel in this respect. They are confident in their ability to interpret whatever exaggeration or distortion of the psychologic panel incurred by the disease process and get at the root of the psychologic characteristics of the peptic ulcer personality as it was prior to the onset of the disease.

The physiologic panel presents the biggest difficulties, especially in the gastro-intestinal aspects. Almost all the work was done at the time of roentgenologically diagnosable ulcer. This has no bearing on the problem because of the altered physiologic state of the stomach and duodenum (and perhaps elsewhere) resulting from the existence of a pathologic lesion there. As an indirect approach to the solution of this difficulty, Meyer, Maskin and Necheles[80] have investigated certain characteristics of the asymptomatic members of families of ulcer patients.

In discussing the component panels of the peptic ulcer terrain, a modified plan of organization after Pende[92] and Draper[29,35] is used here. It consists of three panels: morphologic, psychologic and physiologic. The latter is meant to include Draper's immunologic panel, but since no work has been done along this line, its inclusion obviously adds nothing.

1. The Morphologic Panel. In interpreting the correlation of the morphologic characteristics with gastric and duodenal ulcer, there must be a compromise with absolutism. One cannot expect 100% of gastric ulcer cases to be of one habitus and 100% of duodenal ulcer cases to be of another. There is no fixed and closed pattern; anyone may get peptic ulcer—it is a tendency toward some morphologic form among gastric and duodenal ulcer cases for which we are looking. Robinson says "Every patient does not have to be of the type but it is only necessary to show a predominance of one or many of the gross measures of build in certain diseases to show a constitutional factor."[103]

Many investigators have worked on the problem and it is not easy to survey and interpret their work. Two factors cloud their results: (a) Anthropometric and statistical methods have not been universally used. Some authors have used merely descriptive methods. Others have not laid their work open to statistical analysis. Anthropometric terminology is confusing because of its multiplicity.[23] (b) Peptic ulcer has only recently been considered as constituting two discrete diseases—gastric ulcer and duodenal ulcer. Morphologic patterns were established by some for the peptic ulcer type or the gastro-duodenal ulcer type without regard to site. Since duodenal ulcer occurs from 4 to 10 times as frequently clinically as gastric ulcer, all work done on a random sample of ulcer cases without regard to site would be influenced in the direction of the duodenal ulcer type, assuming it is different in some morphologic respects from the gastric ulcer type.

The Evidence Against a Morphologic Correlation. 1. Of those who regarded peptic ulcer as a unit and without regard for the ulcer site, Aschner,[32b] Udaondo[103a] and Hegemann[21b,45c] concluded there was no typical ulcer habitus. Hegemann condemns the predisposition to ulcer by the asthenic habitus.

2. Miller,[36] working on the correlation of gastric ulcer with the asthenic

habitus (the more recent concept) found only 35% asthenics in his series. This, however, was submitted to no further statistical analysis. In this same article, however, Miller expresses his acceptance of the concept of constitutional background in peptic ulcer and agrees that it separates peptic ulcer into gastric ulcer (as distinct from) and duodenal ulcer.

3. Feigenbaum and Howat[43,44] criticize physiognomic correlation with peptic ulcer on the ground that the disease itself may be responsible for the observed characteristics. The answer to this has been given above (see pages 94–95).

4. The data of Feigenbaum and Howat[43,44] are commensurate with Draper's but the authors are led to different conclusion because they used a different statistical approach. They used the standard error and significant difference technique and claimed that graphic figures alone cannot be accepted. From their study, they concluded that there is no anatomic characteristic distinctive of patients with peptic ulcer and that too much importance has been placed upon the rôle of physical constitution in the etiology of disease.

Robinson and Brucer[103] answer them specifically by stating that the measurements not showing significant differences in their series are those which have no bearing on gross build and that those measurements which do have such bearing, confirm and corroborate Draper's work.

The work of those who find no correlation between some morphologic pattern and gastric and duodenal ulcer is in the minority and the bulk of the work overwhelmingly points to a correlation. Fiegenbaum and Howat have been answered adequately by Robinson and Brucer and by the use of measurements which are independent of the disease process or which are qualified, if under the influence of the disease, so as to render them under the domain of the ulcer predisposition period.

Evidence for a Morphologic Correlation. As has been stated, the great majority of workers in the field agree that there is a morphologic type predisposed to ulcer, but unfortunately, they are not in complete accord as to the physiognomic pattern.

A great amount of detailed anthropometric work has been done but it is not the purpose of this paper to present it in detail or in tabular form. The main outlines and substance only will be considered.

Facial characteristics appear to be common to gastric and duodenal ulcer. It is to the work of Draper and his associates that much of this is due. Stenbuck[113] and Caroli and Corman[15] have emphasized the facies of ulcer patients as of diagnostic value but it should be pointed out here that they admitted the effect of the disease on the facies and therefore, their contributions in the direction of this paper must be considered in that light. Draper's measurements of fixed points are of more value here.

Some of Draper's work was done by comparing the gastric and duodenal ulcer head and face with those of several other disease-races, *viz.*, nephritic hypertension, tuberculosis, primary pernicious anemia, and gall bladder disease.[34] Various anthropometric indices were used and the ulcer patient was found to be intermediate in all respects to the other disease-races whether his ulcer was on the gastric or duodenal side of the pylorus. In this study, the statistical methods employed were accumulative percentage frequency curves and averages of the various indices.

The facial design is not as different and as distinctively pathognomonic from that of the average human being as to strike a distinctive picture in one's mind immediately, but it can be recognized.[32] The keystone is a hexagonal figure formed by the nasolabial folds, chin, and nose.[113] The main facial proportions are such as to suggest a slightly wide upper half

above a small tapering chin.[29,32] Disproportionately increased mesomorphy in the head and neck has been found by Sheldon.[108] High malar prominences are seen which give emphasis to the anxious, energetic and interested demeanor.[26] There is a happy relationship between the interpupillary space and facial diameter[29,32] and the palpebràl fissures are widened sufficiently in most cases to show some sclera above the iris.[32]

There is disagreement between Draper and Stenbuck on the ulcer nose. Stenbuck[113] describes it as straight, of variable length, and emphasizes its lack of prominence, whereas Draper[26,29] attributes a long, thin nose to the ulcer male (low nasal index) and a shorter and wider nose to the ulcer female (high nasal index).

Other characteristic findings are lateral incisors which are smaller than the central incisors, a sharp biting edge of the teeth, an extremely hard consistency of the teeth, labial version of the incisors continuous with the slope of the plate, an upper jaw which is marked by a deep palate, a narrow round anterior arch set with teeth of irregular size, a curing occlusion line, upper median incisors which project over the two lateral incisors, an acute angle of the mandible, a very short horizontal mandibular ramus, and a chin big in all directions.[26,29,31,35,113]

As to the gastric and duodenal ulcer habitus, there is not the degree of accord that exists in consideration of the facies.

The most widely accepted viewpoint is that gastric ulcer cases are more often associated with an asthenic habitus whereas duodenal ulcer cases are associated frequently with a hypersthenic type of body form.

Stiller[53a] made brief mention that the asthenic habitus predisposes to gastric ulcer. Caroli and Corman[15] found 62% of a series of ulcer patients belonging to the linear type habitus with a certain number of the remainder, however, diverging very sharply from this morphologic type and belonging to the opposite—the broad hypersthenic brevilinear type. These latter, they found, have duodenal ulcers which are least indurated. Between these two extremes of bodily pattern, these men found intermediary types from which they draw the general principle that the more the linear morphologic type tends toward the lateral, the greater is the frequency of localization of the ulcer in the duodenum and the less pronounced the tendency toward cicatrization. Unfortunately, no further statistical approach was used besides the percentile grouping.

The fundamental concepts in this school of thought spring from Hurst. Hurst and Stewart[66] say "As the special facial characteristics discovered by Draper appear to be common to gastric and duodenal ulcer, whereas the special diathesis which determines the localization of the ulcer appears to be associated with characteristic forms of bodily habitus." Hurst has presented us with the following tabulated concept of a hyposthenic gastric diathesis and a hypersthenic gastric diathesis:[59,63,64,66]

Hyposthenic Gastric Diathesis	*Hypersthenic Gastric Diathesis*
Asthenic habitus	Hypersthenic habitus
Long chest	Short chest
Narrow intercostal angle	Wide intercostal angle
Stomach in vertical position the pyloric portion steeply ascending —the so-called "dropped stomach"	Diagonal or almost horizontal position of stomach—the so-called "hypertonic" or "fishhook" stomach
Predisposes to gastric ulcer	Predisposes to duodenal ulcer
Physiologic properties given below (page 105)	Physiologic properties given later (page 105)

Another point of morphologic differentiation between the gastric and duodenal ulcer individual is given us by Sheldon *et al.*[108] Gynandromorphy is conspicuously absent in cases of gastric ulcer and upon arranging the patients in descending order of the g-index (secondary indications of bisexuality on a seven point scale), the lesion was found to move from far out in the duodenum steadily inward toward the stomach. Draper, on the other hand, finds subtle indications of the component of the opposite sex in body form in both the duodenal and gastric ulcer groups, supporting his belief that the ulcer patient, independent of the site of the ulcer, is an androgynous mosaic.[32]

Although Hurst and Stewart[66] claim that the hyperstenic gastric diathesis is present in almost 100% of duodenal ulcer cases, little anthropometric work has been done by the supporters of this school and similarly is found the lack of more exact and discriminating statistical methods. The concept of the association of the duodenal and gastric ulcer people with extremes of habitus has found agreement in theory by Norman,[89] Brugsch,[89u] Bauer,[89b] Held and Goldbloom,[54] Schneyer,[107] and Miller.[36]

It is difficult to interpret the results of Da Costa and Silva.[23] They found ulcer among "brevilinears" localized 84.2% in the pyloroduodenal region and among "longilinears" localized 67.7% along the lesser curvature. They do not use these terms synonymously with hypersthenic and hyposthenic, for in the same paper[23] it is reported that among both types of ulcers hypersthenicity is very frequent with only 13% of duodenal ulcers and 10% of gastric ulcers being hyposthenics. In addition to confusion in nomenclature, there is the difficulty that no further statistical methods were employed against a control group.

If a random sample of peptic ulcer cases were taken independent of the ulcer site and examined morphologically, on the basis of our last discussion and of the 4 to 10 times greater occurrence of duodenal ulcer, it would be anticipated that the average would be a person fairly close to the hyperesthenic extreme. But this is not always the case. Pende,[92] who says peptic ulcer is an exquisitely constitutional disease, finds, however, that peptic ulcer patients independent of the site of the lesion often correspond to a certain endocrinologic variety of his asthenic microsplanchnic type. Draper[29] (who stands "in the middle of the road" between those who claim that the peptic ulcer race as a whole tends toward the asthenic habitus and those who see a distinct habitus for gastric and duodenal ulcer respectively), who does appreciate the ulcer site in the patients he observes, says that the ulcer patient is of slender build though not necessarily conforming to the asthenic habitus, the leptothymic of Kretschmer,[72] the hyperontomorph of Bean,[8] the linear type of Stockard,[116] the long-thin of Hippocrates, the microsplanchnic of Pende,[92] and so forth. Detailed accounts of these latter may be found elsewhere along with analyses of their physical, mental and physiologic components.[8,12,17,72,82,92,93,94,95,131]

Draper's anthropometric technique is most exact but he restricted his statistical methods to accumulative frequency curves and to the comparison of mean values. Robinson and Brucer[102,103] have used more satisfactory statistical methods but unfortunately ignored the site of the ulcer in their series. They reported that the ulcer patient tended to be of the asthenic, slender-built, long-thin habitus. In fact, no hypersthenics were found in their series of 70 cases. Robinson concludes[102] "The lateral or broad-chested person escapes ulcer." In his series using a large control group, the average (which is anticipated on the basis of the Hurst concept and the random assortment of ulcer cases to be on the hypersthenic side)

differed significantly in the asthenic direction with respect to the ponderal index and chest-height index. Both of these are fundamental indices.

As has been mentioned, Draper takes the "middle of the road" course. While he did say that the peptic ulcer "race" as a whole tended toward the asthenic habitus, he does find differences between the gastric and duodenal patients in the direction of the Hurst school. He says that, in general, duodenal ulcer cases present the same morphologic pattern but almost every detail is slightly heavier or coarser.[26,29,32] Draper[29] says ".... indeed, this coarser or denser quality is seen more or less generally throughout the body and may sometimes aid in detecting the position of the ulcer." In another paper[26] he finds these differences of sufficient specificity and magnitude to claim their utility "almost beyond error" in locating the ulcer site as gastric or duodenal. These criteria may be found there. The chief differences that Draper finds are these: The duodenal ulcer patient has a more thickly set trunk, a subcostal angle not so consistently narrow, extremities less eunuchoidal and less lanky, hands not so gracile, nails squarer, flatter, smaller, and with absent lunulæ, and occasionally a higher ponderal index.

Tscherning[32c] and Ruhmann[32a] agree with Draper that peptic ulcer occurs chiefly in the ranks of the linear type with certain admixtures of the lateral.

Certain local morphologic characteristics may occur in gastric and duodenal ulcer patients. These have not been correlated with an entire diathetic ensemble, nor have they been discussed with regard to incidence, thereby making their rôle highly speculative and problematic. One of these local conditions is the occurrence of aberrant or ectopic intestinal epithelium in parts of the stomach.[54] O. Müller[21c] finds the anatomic characterization of his vasoneurotic diathesis in the neighborhood of the ulceration. Melchior[53b] postulates a duodenal diathesis or constitutional inferiority of the duodenum in which relative atresia, an embryologic anomaly, plays a rôle.

Discussion of the local blood supply to the ulcer regions can be found by Reeves,[95] Wilkie,[123] Robertson and Hargis,[99] and others.[74,77] The critical area of the first portion of the duodenum, from the vascular point of view, is supplied by a variable artery of the end-artery type, the supraduodenal artery. Wilkie[123] speculates as to the possibility of duodenal ulcer being more commonly met with in individuals in whom the supraduodenal arises at a high level, running vertically downward to the duodenum and thereby becoming more liable to strain and narrowing of its lumen. He offers clinical evidence for this. Reeves[95] says that the arrangement of the plexus of vessels in the submucosa of the stomach and duodenum is such that increased resistance to blood flow occurs with subsequent slowing of arteriolar current and predisposition thereby to thrombotic and embolic phenomena. Deviations from the normal which are excessive in this respect may predispose to ulcer, Reeves speculates.

The field may be summarized as follows: 1. No absolutism of correlation exists between gastric and duodenal ulcer patients and some morphologic form.

2. The ulcer facies including expression and anthropometric qualities is common to both gastric and duodenal ulcer.

3. The most widely accepted concept is that gastric ulcer is associated with the hyposthenic gastric diathesis and duodenal ulcer with the hypersthenic gastric diathesis.

Unfortunately this concept needs more exact anthropometric and statistical studies than those that have been done. It certainly offers the

most satisfactory explanation for the mechanism of ulcer localization. The principle governing intermediary types as indicated by Caroli and Corman and the differences observed between the gastric and duodenal ulcer habitus by Draper give partial support to this concept.

Robinson's observations which rest on the most sound statistical analysis and upon a large series, in which, however, no attention was paid to the ulcer site, indicates that the peptic ulcer group as a whole is associated with the asthenic habitus. We must assume that this series was a random one without an abnormal predominance of gastric ulcer cases.

4. Certain local constitutional phenomena have been presented but their rôle in peptic ulcer is still problematical.

In order to definitely settle the problem, new series should be studied with attention given to the ulcer site. The standard error and statistically significant technique must be used to establish the validity and significance of the differences between the gastric and duodenal ulcer habitus. Five fundamental anthropometric indices would be sufficient. Some of the work already done might be amenable to further statistical evaluation. It is only then that Robinson's series could be tested and Hurst's diathetic extremes placed on more firm ground.

2. THE PSYCHOLOGIC PANEL. "The personality of the patient is the inciter to the ulcer and its exacerbations, and is the soil on which the seeds of ulcer mature."[50] Peptic ulcer displays unique selectivity in this panel. Robinson[100] says the outstanding fact about an ulcer patient is his temperament and that only those individuals with a specific inherited susceptibility will succumb to peptic ulcer, those of us with a well-defined type of emotional instability.

A striking uniformity of temperament is noted; the lethargic ulcer patient is a rarity. Ulcer is found in individuals who are under a constant nervous and mental strain or whose psychologic makeup is such that they impose such an environment and mental state on themselves by virtue of their intensively ambitious and driving traits. When we observe them in any of their activities, we find them keen, intelligent, attentive and active.[2,3,42,73,97,98] They are high strung and emotional without the capacity to relax.[22,121] Being jittery, hyperkinetic, hyperirritable and hyperexcitable, they frequently appear a bit stimulated, often resembling patients with a mild hyperthyroidism.[23,42,97,102]

Although of *apparent* independence and of the "wide-awake," "go-getter" type, and at the same time extremely efficient and persistent, they are frequently frustrated in the pursuit of their activities by their too labile energy supply.[18,31,83,100] Their quick fatigability and little endurance necessitates frequent rest periods which, when combined with food and relief from anxiety, promptly rehabilitates them.[31] Because of this fluctuating capacity for activity, they attempt new activities all the time in an attempt to avoid fatigue through new stimulation and so we find the outlet of their energy not poured into a single concentrated channel but scattered in several enterprises.[100,102]

Adding more to their frustration are their standards of perfectionism and conscientiousness which fasten their attention to their projects and allow for no mental relaxation when physical fatigue ensues.[83,97,102] On occasion, however, goaded by their high standards, they are capable of unusual physical and mental performance of a sustained nature and this enables them to do certain things exceedingly well but always at the expense of physical requirements and mental relaxation.[85,95,100]

Hartman[50] says that the ulcer psychologic panel implies a man who is

faced with obstacles that prove to him a trial and a handicap but which he must endeavor to overcome because of his perfectionist, conscientious and ambitious self-driving nature. He then finds himself with more responsibility than he is able to carry and, as a result, exhausts himself mentally and physically with the synchronous exacerbation of the ulcer syndrome.[102] Rivers[97] attributes part of the assumption of unusual responsibility to the success they achieve by dint of their intensive ambition and drive, and adds that the outcome of this forces on them a persistently tense environment rich in mental strain. This is corroborated elsewhere.[85]

His psychic dynamics are on the hyperactive side. Alvarez[3] says: " . . . . in many cases, the tendency to the formation of ulcers is based on the abnormally high reactivity of the individual." Hypersensitivity, reduced mood stability, rapid expenditure of emotional energy, overactive psychomotor activity and a strong hysterical trend are dominant in the picture.[17,31,32d,102] Clasen[17] claims that psychic imbalance exists in our ulcer friend and leads to personal and environmental dysharmony.

The ulcer patient responds too vehemently to little things that disturb his every-day pattern and routine.[3] The patients themselves admit taking things too seriously. Casuality does not belong to them whether it be routine work, relationships with people, or a critical event.

Being timid, fearful, gullible, overprecise, apprehensive, hesitant, sanguine, suspicious, hyperintrospective and easily excitable, events which would roll off a person of more extrovert and self-confident nature, upset and worry the ulcer personality.[31,98] Worry dominates his person.

These are not all seen on the surface. Whether it is his self-consciousness and extreme sensitivity or mass pressure that controls his outward emotional display, our ulcer patient shows external emotional control.[37,100] This is coupled with sustained reaction to psychic trauma.[101] He is marked by emotional continence and thereby becomes labeled distant, shy, reserved, cold, etc. When his temper is ultimately released in outward expression, it is violent, and, interestingly enough, associated with marked visceral dysfunction.[100] Like all the highly introspective, he acts well within the figments of his imagination but his hesitancy in actuality is extreme.[37,102] His self-consciousness manufactures the weights that hang on his mind and he appears glum and serious—the world is watching him, his lack of grace, his inadequacies. It is said by S. C. Robinson[102] that the calm exterior of the ulcer patient covers vegetative stimulation on a subconscious level.

Many observers have further analyzed the depths of the psychic panel. From Mittelmann and Wolff:[83] peptic ulcer people "commonly showed assertive independence and self-sufficiency covering underlying anxiety and insecurity and accompanied by feelings of resentment and hostility." Basically, there are feelings of insecurity and dependence but these are disguised and compensated for by perfectionism and a show of independence and the assumption of excess responsibility.[83] Draper and Touraine[32] report an androgynous situation within both sexes of the ulcer group which results in obvious conflict with environment, maladjustment, and chronic anxiety from the individual's sensitiveness to the component of the other sex in his personality. The male members of the ulcer sex have a strong heterosexual urge whereas the female ulcer people do not.[31,100]

Alexander,[2] while stressing the importance of the psychologic terrain on which the emotions play, finds intaking and incorporative tendencies most conspicuous in peptic ulcer people and these are fought against by

the patient because of their connection with a sense of guilt and inferiority leading to their denial. Alexander then assumes that the stomach symptoms are conditioned by the repressed and pent-up receptive and aggressive taking tendencies which serve as chronic psychic stimuli of stomach function.

Miscellaneous psychologic investigations find the ulcer personality well equipped with qualities that make them good opportunists, while not gifted in the fields of executive ability and planning capacity.[31]

The electroencephalogram has been applied to peptic ulcer patients.[104] Two groups of records resulted. The majority exhibited a dominant Alpha record $3\frac{1}{2}$ times greater than in the normal control group. This is enough for a definite correlation to be made between peptic ulcer and a dominant Alpha record which in turn is correlated with passive, receptive, dependent types of people. This is fairly in accord with the personality arrived at on analysis of the peptic ulcer psychologic terrain.[83]

The remainder of the patients fell into the low Alpha group who exhibit a reactive and opposite personality structure than the above.

3. THE PHYSIOLOGIC PANEL. All observers agree that some imbalance exists in the autonomic-endocrine equilibrium. So complex and basic a problem cannot be ascertained in the short time that study has been devoted to it. General terms such as "lability" and "hyperexcitability" of the autonomic nervous system are accepted but the specific qualitative nature of the problem along with its extent is still undecided.

Durante[37] states: "There is no pathological function of the gastro-intestinal tract that cannot be produced by enhanced innervation." Eppinger and Hess[39] say "Many diseased states including gastric ulcer are associated with autonomic stimulation and the possibility exists that a constitutional tendency of the organism's reacting in a definite way to such stimulation may lie at the root of the matter."

Specifically, the predominant conception is that of vagotonia. An analogy has been drawn between the peptic ulcer syndrome and that of vagotonia.[109] Cushing finds nervous instability, characterized as vagotonia, characteristic of the peptic ulcer terrain.[22] This state of vagotonia has been said to arise from several sources, hyperirritability of the vagus,[17] inadequacy of the sympathetic nervous system,[32] and quick fatigability of the sympathetic nervous system under prolonged stimulation with resulting vagal dominance.[45b]

We will now present the experimental evidence both *pro* and *con* in reference to a state of vagotonia as part of the physiologic terrain of peptic ulcer.

Evidence Favoring Vagotonia. 1. Experimental production of ulcer by damaging the vagus, the sympathetic, the celiac axis, and so forth.[11] Stimulation of the vagus produces the phenomena of gastro-intestinal pathology seen in ulcer.[39]

2. Stigmata of vagotonia: (*a*) Facial pallor in 60% of Westphal's ulcer patients.[21d] (*b*) Cold and sweaty palms and soles in 60%.[21c] (*c*) Certain electrocardiographic signs (Draper and associates[33]). (*d*) Low systolic blood pressure.[76,103] (*e*) Pulse slow to normal.[103] (*f*) Gastro-intestinal phenomena characteristic of increased vagal tone.[11,17,21,26,92,103] (*g*) Exophthalmos.[107] (*h*) Dermographism.[107] (*i*) Vasomotor disturbances.[107] (*j*) The Aschner phenomenon in a large percentage of cases (Peritz and Fleischer[45d]). (*k*) Various cardiovascular phenomena.[26] (*l*) Vagotonic response to adrenalin[21] and to other drugs.[39,56] (*m*) Exaggerated peripheral reflexes.[21] (*n*) Spasmophilic disposition (Peritz and Fleischer[21f]). (*o*) Absence of tremor.[103]

3. Ulcer occurs in early life, a time when vagotonicity normally predominates.[54]

4. The vagotonic state persists after the healing of the initial ulcer while the neurogenic secretory and motor disturbances continue.[25]

5. De Langen[21a] interprets absence of ulcer in Javanese natives as being due to the fact that most of them were sympathicotonics.

6. Seasonal exacerbation simultaneously with the seasonal fluctuation of vagus irritability.[11]

Evidence Against Vagotonia. 1. Existence of mixed stigmata, *i. e.*, stigmata due to sympathicotonia existed simultaneously with others due to vagotonia.[33,86,103] Draper *et al.*[33] explain this by saying that the entire autonomic nervous system in people with the ulcer constitution is in high tension and is labile but that there is a special emphasis upon the parasympathetic division.

2. Cases of marked vagal involvement have been found where *no* gastric or duodenal ulcer was concomitantly found.[11]

3. The stigmata characteristic of vagotonics are not all corroborated by experimental work: (*a*) Winkelstein found exaggerated responses to adrenalin and atropine.[126] (*b*) The dermographic reaction time of peptic ulcer patients was not significantly different from a normal control group.[88] The authors suggest that this contradicts a generalized neurospastic tendency of the blood-vessels. (*c*) Necheles and Levitsky,[86] repeating the experiment of salivary response to pilocarpine in peptic ulcer patients, found the response of the ulcer group significantly lower than that of the normal control group. This speaks against generalized vagotonia. The concept does exist that vagotonia may be generalized or localized.[39] (*d*) Winkelstein finds the excessive response of the peptic ulcer group to mechanical, electrical and pharmacologic stimulation indicative of a *labile* vegetative nervous system and *not of a disturbed or imbalanced* nervous system.[125,127] This overirritability persists after surgical cure suggesting a general bodily state.[125] (*e*) Low blood pressure is not always found. Steigmann[112] and Hurst[59] report systolic readings which are 10 to 20 mm. of mercury higher than Robinson and Brucer's readings.[102,103]

The *pro* and *con* on vagotonia as part of the physiologic panel of peptic ulcer leaves the matter in an unsatisfactory state. Much experimental work must be done and repeated. The possibility of effects of the disease process must be taken into account. Generalized vagotonia probably does not exist in the majority of ulcer cases. A labile vegetative nervous system is typical of the peptic ulcer physiologic panel. Whether localized vagotonia exists in various areas is still problematical. In this regard Necheles and Levitsky[86] suggest the interesting concept that certain centers in the brain may be in a state of increased activity while others are depressed, normal or reflexly inhibited, *c. g.*, the salivary center may be depressed while the gastric acidity secretion center may be hyperactive.

This general instability of the autonomic nervous system is evidenced by the vasoneurotic diathesis of Müller and Heimberger[66a] in which peptic ulcer patients show a congenital and often inherited condition of dysharmony of the peripheral vessels and vessels of the gastric mucosa. They come to this conclusion through histologic examination of these blood-vessels when they observed great irregularity in course, caliber and anastomoses as well as of tone, of the arterioles, venules and capillaries. Yet, when put to a physiologic test, a dermographic reaction time experiment revealed no spastic tendency in peripheral blood-vessels.[88] Sustained nervous reaction time has been found characteristic.[103]

4. Petersen and Levinson,[94] working on 3 cases of peptic ulcer (and therefore results are to be taken with reserve) report an increased b.m.r., a more irritable musculature, a slightly decreased carbon dioxide combining power of the serum, higher resistance of the skin to electric current and longer Kromayer light reaction time. Robinson,[103] however, reporting on more cases, finds the b.m.r. low to normal.

5. Leukocytes normal,[103] blood cholesterol normal,[103] calcium blood level normal,[127] gastric ulcer has a hemoglobin of 75% and duodenal ulcer of 90% without hematemesis or melena.[66]

6. Electroencephalogram reports show the majority of peptic ulcer patients with a dominant Alpha record and the remainder falling into the low Alpha group.

7. The ECG correlates have been reported as a shorter P–R interval, an extremely long Q–T interval, sinus arrhythmias commoner than in normals especially in the third and fourth decades, pulse rate slower than normal especially in the fifth decade, and a curve that is steep and abrupt.[33]

The gastric and duodenal ulcer constitutions are far from complete. The work that has been done is not all satisfactory because of the disregard for the ulcer site and the inattention to the changes in the various panels effected through the disease process. The greatest lack lies in a statistical correlation between the panels themselves. The psychologic panel seems common to both gastric and duodenal ulcer diatheses and yet it is unknown how it is statistically correlated with the gastric and duodenal ulcer varieties of habitus and physiology. Hurst's diathetic ensemble embraces morphologic and physiologic components, but leaves the psychologic untouched. This work is needed to provide more specific evidence for the genetic mechanics involved, such as linkage, and to firmly establish the gastric and duodenal ulcer terrains as entire diathetic ensembles.

D. Relation to Pathogenesis. For the sake of simplicity, the peptic ulcer disease state can be expressed algebraically as $a = bc$, where a is the peptic ulcer state, b, environment, and c, the congenital terrain. This paper has dealt with the diathetic terrain of peptic ulcer and not with environmental factors. In no way were we trying to minimize the rôle of the latter and overemphasize that of the former. The above simplified expression is a product: an individual with a highly fertile soil will escape ulcer if environmental stress and tension are negligible; the converse is true when the terrain is barren.

The following brief review will concern the possible relationship of the peptic ulcer terrain to the pathogenesis of this condition. The manuscript will not deal with the controversies of the pathogenesis of peptic ulcer. In the broadest sense, peptic ulcer can be looked upon as a duel between the resistance of the mucosa and the aggression of mechanico-chemical factors. In light of current theories, it will be pointed out how the peptic ulcer constitution decreases the resistance of the ulcer-bearing tissues or increases the aggressiveness of these mechanico-chemical factors.

1. INDIRECT OF GENETIC RELATIONSHIP. It is generally agreed that peptic ulcer is but a local manifestation of a systemic state and thus, the rôle of systemic orientation has been emphasized.[5,7,29,30,35c,36,45,47,54,96,101,127] Peptic ulcer is viewed as a local secondary phenomenon, secondary to systemic predisposition.[6,56,59,101,109] Winkelstein[125] has put it aptly— "Given, for example, an individual often of a certain morphologic type, in a family predisposed to the ulcer disease, with tissues that react unfavor-

ably to exogenous trauma, with a labile vegetative nervous system which initiates or exaggerates the unfavorable tissue responses, with a stomach that secretes an eroding gastric juice, an individual who reacts unfavorably to exogenous strain, we have most of the constitutional conditions entering into recurrent peptic ulcer formation."

General correlation of characteristics in people predisposed to diseases has been mentioned.[8] Barker[4] presents the general concept of constitutional grouping with correlation of characteristics including physiologic and emotional responses, and resistance to disease processes. Specifically,[35] in peptic ulcer patients, there have been found frequent enough repetitions of combinations of characteristics that the observers were enabled to predict other panels with great correctness, on the basis of their knowledge of one panel.

The tendency of characteristics to remain in their original combination is not a new phenomenon. The genetic mechanism of linkage explains this. In linkage, genes on the same chromosome tend to remain together, the more so as they are physically closer together and therefore the characteristics dependent on such genes remain together or "linked" accordingly. Linkage is a strong possibility as the underlying mechanism here. Unfortunately, man's large number of chromosomes make him an inconvenient genetic subject and coupled with the lack of interpanel statistical correlation, one cannot be more specific. From the work done, the same psychologic panel seems linked to both hypersthenic and hyposthenic gastric diatheses whereas a different morphophysiologic ensemble seems associated with respective diatheses. Bauer[6] has said that the relationship of the primordial genes may be linked with certain somatic and psychic characteristics which are predisposing to disease.

2. Direct Relationship. Bauer[6] calls this the "pleiotropic" relationship and it consists of fitting in the constitutional characteristics of the ulcer patient in terms of the dynamics of the disease process. This follows below.

(a) *Neurosomatic Elements.* From our previous descriptions, the important characteristics of the ulcer patient, whether duodenal or gastric, which are particularly influential here, are a great lability of the nervous system with possible parasympathetic dominance, a sustained reaction time to psychic stimuli, and easy susceptibility to vasoneurosis. The fundamental concept is set forth by Durante:[37] "The life of the gastric cell is dependent on the integrity of the sympathetic nervous system." Constitutionally predisposed nervous systems have "inherited grooved pathways,"[37] through which psychic trauma plays havoc with the gastric cell. It should be mentioned that this differs markedly from Held's concept of conditioned constitutional status through neural reactions.[52,54] References made above to experimental ulcer production through neural stimulation and other techniques and to psychosomatic studies revealing local intestinal reactions leading to pathologic changes have afforded us corroborative evidence in this direction.

Based on these findings, Rivers,[97,98] Winkelstein,[127] Cushing,[22] Alvarez,[3] Eustermann,[40,41] and many others[11,21,23,25,27,32,37,39,42,45,53,54,55,73,85,101,102,105] have contributed a schema and succession of events in a predisposed individual with neurosomatic and psychosomatic orientations described below:

Predisposing Neurologic Condition: (1) Symbol stimulus through high cortical centers.[27] (2) Vasoneurosis.[54,55] (3) Autonomic stimulation.[23,39] (4) Chronic imbalance of the autonomic nervous system.[102,105] (5) Oversensitive vasomotor instability.[11,25]

Resulting Gastric and Duodenal Phenomena: (1) Bombardment of stimuli on lesser curvature of stomach and first portion of duodenum.[102] (Adequate neural mechanisms exist to explain this and the other phenomena.[130]) (2) Marked vascular spasm in some areas leading to ischemia of the area supplied and which, when continued sufficiently long, allow autodigestion and ulcer formation.[3,21,40,41,54,85,101,102,105] (3) Hemorrhagic areas have been reported also with local ulcer foci resulting.[130] (4) Pyloric spasm, hyperperistalsis, hyperacidity, high pepsin, hypersecretion, increased gastric contents, decreased protective mucin production—all allowing an ulcer or de-epithelialization that has occurred to remain and become chronic.[11,21,23,39,41,73,97,98,127,129] (5) Myospasm clamping off vessels thereby lessening resistance of the mucosa to increased acid and pepsin. (6) Additional steps added in the pathogenesis are gastritis, minor mucosal erosions and abrasions prolonged by the above factors.

It should be mentioned that the predisposed patient has this neural mechanism set off quickly by stimuli not affecting the normal and by symbols and vasoneurotic conditioning. He has them frequently and on a chronic scale due to his chronic vegetative instability. The acute responses to conditioning or psychic trauma are violent and sustained. The persistence of the ulcer in cases of de-epithelialization, which Winkelstein[127] considers a common lesion and heals without scarring in the normal, remains because of the frequent occasion of this chain of events plus chronic factors listed below (*c* and *d*).

(*b*) *Endocrine Elements.* This is still too problematical for any direct mechanism to be invoked in detail.

(*c*) *Local Conditions.* There has been a hypothesis that the susceptibility of the ulcer-bearing areas to disease is out of proportion to that of the rest of the stomach and body tissues.[54] These are given below and it is not yet known what correlation these bear to diathetic ensembles: (1) Tendency to independent localized myospasm producing ischemia and decreased resistance to digestive activity.[92] (2) Tendency to localized vascular spasmophilia[54] which produces the same effect as the above. (3) Abnormal sensitivity of tissue to trauma.[11] (4) Abnormal sensitivity of vessel walls to trauma.[11] (5) Localized endarteritic and arteriosclerotic processes leading to pathologic vascular phenomena.[11,127] (6) Occurrence of aberrant intestinal epithelium on the lesser curvature which is less resistant to gastric secretions than normal gastric mucosa.[7,54] (7) "Duodenal diathesis" of Melchior[53b] in which there is a constitutional inferiority of the duodenum in the form of relative congenital atresia producing a site of local duodenal irritation and predisposing thereby to duodenal ulcer. (8) Status lymphaticus[54] confined to the stomach favoring local invasion by infection. (9) Wilkie[123] and Reeves[95] speak of local circulatory deviations which predispose to narrowing of the lumen and thrombotic and embolic occlusion of the vessels supplying the ulcer areas. (10) Constitutional diminution of mucus of the stomach.[53c] (11) Capillary stasis in the gastric mucosa predisposing to erosion of the mucous membranes.[45c] (12) A local mechanical factor in body form suggested by Schneyer[107] where a deep fold in the abdominal wall occurring in some people in the sitting position may cause continuous irritation and pressure over a certain area and lead to actual ulcer.

The value of these local conditions is limited first by lack of statistical incidence and hence their significance and, second, by the failure of any correlation with a diathetic ensemble of which they might be part and parcel.

(d) *Morphologic and Physiologic Conditions.* These are considered together because of their close linkage as exhibited in the hyposthenic and hypersthenic gastric diatheses of Hurst. By doing this, Rivers' objection[97] is overcome in that the morphologic panel *per se* is meaningless and a more dynamic relationship is indicated. There is, however, another objection that is raised[45f] and which further emphasizes our lack of statistical interpanel correlation, namely, that the genes which determine the physiologic and morphologic characteristics of the stomach are not always closely related to those determining the build of the patient.

The Hurst diatheses are extremes. Our treatment of their rôle in the pathogenesis of peptic ulcer will restrict itself to these extremes and assumes that admixtures of the two diatheses will accordingly be influenced by the balance in one direction or the other. Again, this is a defect in our knowledge, namely, as to what variations occur in physiology and morphology in admixtures of these two diatheses.

These diatheses are just that. They are predisposing to a condition and not immediate etiologic agents. They are compatible with perfect health but in unfavorable circumstances in a person with a nervous system that has been described, each diathesis predisposes to ulcer at a different site.[9,59,60,61,62,82,84]

Hypersthenic gastric diathesis predisposes to duodenal ulcer by: (1) Pouring gastric contents into the duodenum in a hyperacid state causing repeated duodenal irritation. Roentgenologic evidence exists for this and has been deemed actual precursor of duodenal ulcer.[54] (2) Strong acid production, hyperacid, hypersecreting climbing curve maintained as a physiologic characteristic throughout life and independent of the state of the ulcer.[21,61] (3) Less mucus production.[61] (4) Mechanical pressure persistently from neighboring organs explains chronicity and failure to heal.[54] (5) Hyperperistalsis leads to several hours a day when the stomach is devoid of contents except for an acid gastric juice which it pours constantly on the duodenal cap with resulting duodenal irritation.[59,66]

Hyposthenic gastric diathesis predisposes to gastric ulcer by: (1) Relative atony causes delay in emptying time with a tendency to gastric stagnation and irritation.[54] (2) The stomach which is longer than average has a tendency to orthostatic "hour-glass" configuration in which the middle of the stomach forms a definite obstruction to the outward passage of food so long as the erect posture is maintained.[66] This causes an abnormal amount of friction especially on the lesser curvature where most gastric ulcers occur. (3) Tendency to kinking of the duodenum in such people favors ulcer formation by allowing poor neutralization.[11,53] (4) Low acidity characteristic of this diathesis means that the second line of defense against harmful agents is deficient with resulting gastritis or duodenitis which then terminates in ulcer.[61,80] There is some experimental corroboration for this from Ivy.[67,68] (5) Cole[19] found that tension on the terminal branches of the left gastric artery is especially great in hyposthenic people in the erect posture. This is directly concerned with an inadequate blood supply to the area supplied by this vessel, the most common site of gastric ulcer. Pende presents a similar conception.[92]

Summary. Evidence is presented for the existence of an "ulcer type:" and a detailed account of this characteristic is given in the three panels of constitution. The possible relationship of this constitutional terrain to the pathogenesis of gastric and duodenal ulcer has been indicated.

REFERENCES

(1.) Adams, W. P.: South. Med. and Surg., 99, 221, 1937. (2.) Alexander, F., *et al.*: Psycho-analyt. Quart., 3, 501, 1934. (2a.) Hartman, H. R.: Med. Clin. North America, 16, 1366, 1933 (cited by Alexander). (3.) Alvarez, W. C.: Am. J. Surg., 18, 207, 1932.

(4.) Barker, L. F.: Rev. Gastro-enterol., 2, 1, 1935. (5.) Bauer, J.: Internat. Clin., 3, 53, 1941. (6.) Bauer, J.: Bull. Johns Hopkins Hosp., 44, 52, 1929. (7.) Bauer, J.: Rev. Gastro-enterol., 7, 21, 1940. (8.) Bean, B. B.: Bull. Johns Hopkins Hosp., 23, 363, 1912. (9.) Bennett, T. I., and Ryle, J. A.: Guy's Hosp. Rep., 71, 286, 1921. (10.) Bloomfield, A. L., Chen, C. K., and French, L. R.: J. Clin. Invest., 19, 863, 1940. (11.) Boyd, L. J.: J. Am. Inst. Homeopathy, 26, 35, 115, 187, 193, 271, 1933. (12.) Boyd, L. J.: J. Am. Inst. Homeopathy. 24, 71, 165, 397, 698, 962, 1186, 1931. (13.) Brown, P. K.: Calif. and West. Med., 33, 804, 1930. (14.) Brown, W. H.: Arch. Int. Med., 44, 625, 1929.

(15.) Caroli, J., and Corman, L.: Arch. d. des mal de l'app. digest, 25, 26, 1935. (16.) Cheyney, G., and Bloomfield, A. L.: J. Clin. Invest., 5, 511, 1928. (17.) Clasen, A. C.: Ann. Int. Med., 3, 995, 1930. (18.) Clendenning, L.: The Human Body, New York, Alfred A. Knopf, p. 19, 1937. (19.) Cole, L. G.: New England J. Med., 201, 1081, 1929. (20.) Crile, G. W.: Surg., Gynec. and Obst., 40, 818, 1925. (21.) Crohn, B. B.: Affectations of the Stomach, Philadelphia, W. B. Saunders Company, Chapter XXIX, 1927. (21a.) De Langen: Abstr., J. Am. Med. Assn. (cited by Crohn). (21b.) Hegemann, W.: Med. Klin., 38, 181, 1924 (cited by Crohn). (21c.) Müller, O.: Die Kapillaren der Menschlischen Korpero berfläche, Stuttgart, 1922 (cited by Crohn). (21d.) Westphal, K.: Deut. Arch. klin. Med., 114, 327, 1914 (cited by Crohn). (21e.) Ewald, C. A.: Deut. med. Wchnschr., 38, 785, 1912 (cited by Crohn). (21f.) Peritz, G., and Fleischer, F.: Arch. f. Verdaungskr., 32, 243, 1924 (cited by Crohn). (22.) Cushing, H.: Surg., Gynec. and Obst., 55, 1, 1932.

(23.) Da Costa, M. B., and Silva, M. S.: Arch. des mal. de l'app. digest, 29, 977, 1940. (24.) Dauwe, F.: Arch. des mal. de l'app. digest, 7, 375, 1933. (25.) Diamond, J. S.: Am. J. Med. Sci., 173, 548, 1922. (26.) Draper, G.: The Human Constitution, Philadelphia, W. B. Saunders Company, 1924. (27.) Draper, G.: Am. J. Med. Sci., 190, 545, 1935. (28.) Draper, G.: New York State J. Med., 34, 1052, 1934. (29.) Draper, G.: Disease and Man, London, Kegan Paul, 1930. (30.) Draper, G.: Human Constitution, Baltimore, Williams & Wilkins Company, 1928. (31.) Draper, G., and McGraw, R. B.: Am. J. Med. Sci., 175, 299, 1927. (32.) Draper, G., and Touraine, G. A.: Arch. Int. Med., 49, 616, 1932. (32a.) Ruhmann, W.: Der Ulcuskranke: Studien zur Konstitution und Symptomatik am gesamten Status bei chronischen Ulcer pepticum mit besonderer Berücksichtigung des vegetativen Nervensystems, Berlin, S. Karger, 1926 (cited by Draper and Touraine). (32b.) Aschner, B.: Ztschr. f. d. ges. Anat., 9, 6, 1923 (cited by Draper and Touraine). (32c.) Tscherning: Arch. f. Verdaungskr., 31, 351, 1923 (cited by Draper and Touraine). (32d.) Gilles de la Tourette: Semaine méd., 19, 377, 1899 (cited by Draper and Touraine). (33.) Draper, G., Bruenn, H. G., and Dupertuis, C. W.: Am. J. Med. Sci., 194, 514, 1937. (34.) Draper, G., Dunn, H. L., and Segal, D.: Am. J. Med. Sci., 169, 322, 1925. (35.) Draper, G., Dunn, H. L., and Segal, D.: J. Am. Med. Assn., 82, 431, 1924. (36.) Drossner, J. L., and Miller, T. G.: Am. J. Med. Sci., 199, 90, 1940. (37.) Durante, L.: Surg., Gynec. and Obst., 22, 399, 1916.

(38.) Eliason, E. L.: Lectures to third year class in surgery, University of Pennsylvania Medical School. (39.) Eppinger, H., and Hess, L.: Nervous and Mental Disease Monograph Series No. 20, New York, 1915 (translated). (40.) Eustermann, G. B.: J. Med. Soc. New Jersey, 36, 369, 1939. (41.) Eustermann, G. B.: J. Am. Med. Assn., 99, 791, 1922.

(42.) Feldman's reply to a question in a discussion, J. Am. Med. Assn., 120, 284, 1942. (43.) Feigenbaum, J., and Howat, D.: Arch. Int. Med., 55, 445, 1935. (44.) Feigenbaum, J., and Howat, D.: J. Clin. Invest., 13, 121, 1934. (45.) Friedenwald, J.: J. Am. Med. Assn., 95, 905, 1930. (45a.) Nelken: no reference given (cited by Friedenwald). (45b.) von Bergmann: no reference given (cited by Friedenwald). (45c.) Hegemann: no reference given (cited by Friedenwald). (d.) Peritz and Fleischer: no reference given (cited by Friedenwald). (45e.) Danzer: no reference given (cited by Friedenwald). (f.) Alvarez: no reference given (cited by Friedenwald). (46.) Friedman, G. A.: J. Med. Res., 32, 287, 1915. (47.) Friedman, G. A.: J. Am. Med. Assn., 71, 1543, 1918. (48.) Fulton, J. E.: Physiology of the Nervous System. London, Oxford University Press, p. 253, 1938.

(49.) Garin, C., Bernay, P., and Chastel: Lyon méd., 161, 386, 1938.

(50.) Hartman, H. R.: Med. Clin. North America, 16, 1357, 1933. (50a.) Moynihan: reference not given (cited by Hartman). (51.) Hartman, H. R., and Rivers, A. B.: Arch. Int. Med., 44, 314, 1929.

(52.) **Held, I. W.**: Rev. Gastro-enterol., 8, 350, 1941. (53.) **Held, I. W.**: Internat. Clin., 3, 96, 1923. (53a.) **Stiller**: no reference given (cited by Held). (53b.) **Melchior**: Erg. d. Chir. u. Orthop., Berlin, 1911; Zur Diagnostik d. peptischen duodenal Geschürs., Med. Klin., 1912 (cited by Held). (53c.) **Kaufmann, J.**: Arch. f. Verdaungskr., p. 616, 1907 (cited by Held). (54.) **Held, I. W.**, and **Goldbloom**: Med. Clin. North America, 14, 319, 1930. (55.) **Held, I. W.**, and **Roemer, J.**: Am. J. Med. Sci., 164, 188, 1932. (56.) **Highman, S. E.**: South African J. Med. Sci., 5, 20, 1940. (57.) **Hoelzer, F.**: Am. J. Digest. Dis. and Nutr., 9, 188, 1942. (58.) **Hugh, M.**: Brit. Med. J., 2, 235, 1940. (59.) **Hurst, A. F.**: The Constitutional Factor in Disease, London, Kegan Paul, Trench, Trubner & Co., 1927. (59a.) **Balint, R.** (Budapest): Ulcusproblem u. Sauere-basengleichgewicht, Berlin, 1927 (cited by Hurst). (60.) **Hurst, A. F.**: Guy's Hosp. Rep., 77, 22, 1927. (61.) **Hurst, A. F.**: Brit. Med. J., 1, 559, 1920. (62.) **Hurst, A. F.**: Brit. Med. J., 2, 89, 1933. (63.) **Hurst, A. F.**: Lancet, 2, 1369, 1922. (64.) **Hurst, A. F.**: Brit. Med. J., 1, 823, 1927. (65.) **Hurst, A. F.**: Guy's Hosp. Rep., 71, 450, 1921. (66.) **Hurst, A. F.**, and **Stewart, M. J.**: Gastric and Duodenal Ulcer, London, Oxford University Press, 1939. (66a.) **Müller, O.**, and **Heimberger, H.**: Deutsch. Ztschr. f. Chir., 187, 33, 1924 (cited by Hurst and Stewart).

(67.) **Ivy, A. C.**: Arch. Int. Med., 25, 6, 1920. (68.) **Ivy, A. C.**: J. Am. Med. Assn., 75, 1540, 1920.

(69.) **Jennison, J.**: Am. J. Med. Sci., 196, 654, 1938.

. (70.) **Keller, A. D.**, **Hare, W. K.**, and **D'Armour, M. C.**: Proc. Soc. Exp. Biol. and Med., 30, 772, 1933. (71.) **Klein, E.**: Arch. Surg., 26, 235, 1933. (72.) **Kretschmer, E.**: Bodily Habitus and Character, London, Harcourt, Brace & Co., p. 266, 1925 (English translation).

(73.) **Levinson, L. A.**: Ohio State Med. J., 32, 517, 1936.

(74.) **Massie, G.**: Guy's Hosp. Gaz., 35, 374, 1921. (75.) **Masten, M. G.**, and **Bunts, R. C.**: Arch. Int. Med., 54, 916, 1934. (76.) **McGavack, T.**: Med. Clin. North America, 26, 683, 1942. (76a.) **Ask-Upmark, E.**: Acta med. Scand., 103, 280, 1940 (cited by McGavack). (77.) **McGregor, A. L.**: Synopsis of Surgical Anatomy, Baltimore, Williams & Wilkins Company, p. 48, 1939. (78.) **McVicar, C. S.**: Proc. Staff Meet. Mayo Clin., 2, 50, 1927. (79.) **Metz, M. H.**, and **Lackey, R. W.**: Am. J. Digest. Dis. and Nutr., 7, 27, 1940. (80.) **Meyer, J.**, **Maskin, M.**, and **Necheles, H.**: Am. J. Digest. Dis. and Nutr., 3, 474, 1936. (81.) **Miller, T. G.**, **Pendergrass, E. P.**, and **Andrews, A. S.**: Am. J. Med. Sci., 177, 15, 1929. (82.) **Mills, R. W.**: Am. J. Roentgenol., 4, 155, 1917. (83.) **Mittelmann, B.**, and **Wolff, H.**: Psychosomatic Med., 4, 5, 1942. (84.) **Moody, R. O.**, **Van Nuys, R. G.**, and **Chamberlain, W. E.**: J. Am. Med. Assn., 81, 1924, 1923. (85.) **Morrison, S.**, and **Feldman, M.**: J. Am. Med. Assn., 120, 738, 1942.

(86.) **Necheles, H.**, and **Levitsky, P.**: J. Lab. and Clin. Med., 22, 624, 1937. (87.) **Necheles, H.**, and **Maskin, M. H.**: Am. J. Digest. Dis. and Nutr., 3, 90, 1936. (88.) **Necheles, H.**, and **Maskin, M. H.**: Am. J. Digest. Dis. and Nutr., 3, 92, 1936. (89.) **Norman, J.**: Med. Rec., 147, 498, 1938. (89a.) **Brugsch**: no reference given (cited by Norman). (89b.) **Bauer**: no reference given (cited by Norman).

(90.) **Ophuls, W.**: J. Exp. Med., 8, 181, 1906.

(91.) **Palmer, D. H.**: Ohio State Med. J., 35, 717, 1939. (92.) **Pende, N.**: Constitutional Inadequacies, Philadelphia, Lea & Febiger, 1928 (translated by Naccarati). (93.) **Petersen, W. F.**: Physiol. Rev., 12, 283, 1932. (94.) **Petersen, W. F.**, and **Levinson, S. A.**: Arch. Path., 9, 151, 1930.

(95.) **Reeves, T. B.**: Surg., Gynec. and Obst., 30, 374, 1920. (96.) **Riecker, H.**: Ann. Int. Med., 7, 732, 1933. (97.) **Rivers, A. B.**: Arch. Int. Med., 53, 97, 1934. (98.) **Rivers, A. B.**: J. Mt. Sinai Hosp., 4, 167, 1937. (99.) **Robertson, H. E.**, and **Hargis, E. H.**: Med. Clin. North America, 8, 1065, 1925. (100.) **Robinson, S. C.**: Med. Press, 201, 26, 1939. (101.) **Robinson, S. C.**: Illinois Med. J., 73, 210, 1938. (102.) **Robinson, S. C.**: Am. J. Digest. Dis. and Nutr., 2, 333, 1935. (103.) **Robinson, S. C.**, and **Brucer, M.**: Am. J. Digest. Dis. and Nutr., 7, 365, 1940. (103a.) **Udaondo, C. B.**: Arch. des mal. de l'app. digest., 18, 841, 1928 (cited by Robinson and Brucer). (104.) **Rubin, S.**, and **Bowman, K. M.**: Psychosomatic Med., 4, 309, 1942. (105.) **Russell, G. M.**: Rev. Gastro-enterol., 8, 114, 1941.

(106.) **Sandweiss, Saltzstein and Farbman**: Am. J. Digest. Dis. and Nutr., 6, 11, 1939. (107.) **Schneyer, J.**: Med. Rec., 140, 672, 1934. (108.) **Sheldon, W. H.**, **Stevens, S. S.**, and **Tucker, W. B.**: The Varieties of Human Physique, New York and London, Harper & Bros., 1940. (109.) **Simpson, V. E.**: Kentucky Med. J., 26, 105, 1928. (109a.) **Koehler**: reference not given (cited by Simpson). (110.) **Smith, D.**: Brit. Med. J., 2, 293, 1928. (111.) **Smithies, F.**: Am. J. Digest. Dis. and Nutr., 1, 75, 1935. (112.) **Steigmann, F.**: Am. J. Digest. Dis. and Nutr., 3, 310, 1936. (113.) **Stenbuck, J. B.**: Am. J. Surg., 38, 181, 1924. (114.) **Stewart, M. J.**: Lancet, 2, 565, 1931. (115.) **Stockard, C. R.**: Medicine, 5, 105, 1926. (116.) **Stockard, C. R.**: Harvey Lectures, 1, 23, 1923. (117.) **Sturtevant, M.**, and **Shapiro, L. L.**: Arch. Int. Med., 38, 41, 1926.

(118.) Turner, E. L., and Latuff, A. G.: La presse méd., 43, 339, 1935.   (119.) Tucker, W. B., and Lessa, W. A.: Quart. Rev. Biol., 15, 265, 1940.   (120.) Tucker, W. B., and Lessa, W. A.: Quart. Rev. Biol., 15, 411, 1940.

(121.) Upham, R.: J. Am. Inst. Homeopathy, 28, 744, 1935.

(122.) Vanzant, F. R., Alvarez, W. C., Eustermann, G. B., and Berkson: Arch. Int. Med., 52, 616, 1933.

(123.) Wilkie, D. P. D.: Surg., Gynec. and Obst., 13, 399, 1911.   (124.) Willcox, R. H.: Brit. Med. J., 1, 1008, 1940.   (125.) Winkelstein, A.: Am. J. Med. Sci., 185, 695, 1933.   (126.) Winkelstein, A.: Arch. Int. Med., 37, 541, 1926.   (127.) Winkelstein, A.: Arch. Int. Med., 37, 541, 1926.   (128.) Winkelstein, A.: J. Mt. Sinai Hosp., 7, 29, 1940.

(129.) Wittkower, E.: J. Ment. Sci., 81, 533, 1935.   (130.) Wolf, S., and Wolff, H. G.: J. Am. Med. Assn., 120, 670, 1942.   (131.) Wroczynski, C.: Bull. Health Organ, League of Nations, 6, 551, 1937.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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MILITARY PSYCHIATRY—A SUMMARY OF SOME OF THE LITERATURE

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This review aims to correlate the various opinions expressed in the extensive literature of military psychiatry. This broad field is considered under the following topics:

1. The importance of psychiatry in military medicine as judged by past experience, chiefly World War I.

2. The examination and selection of men for the armed forces.

3. The psychiatric problems of the armed forces.

4. The rehabilitation of psychiatric casualties after rejection at the induction center examination or after separation from service in the armed forces.

I. Neuropsychiatric Casualties of World War I. A consideration of the literature regarding neuropsychiatric casualties of World War I reveals that there was an unexpected prominence of neuropsychiatric problems in the services, and in July, 1918, General Pershing sent the following cablegram from overseas: "Prominence of mental disorders in replacement troops recently received suggests urgent importance of intensive efforts in eliminating mentally unfit from organization of the new draft prior to departure from the United States."[30]

Pearce Bailey, a co-author of Volume X of the official history of the Medical Department of the Army in the World War, remarked, "There was passive, and even active antagonism to neuropsychiatric examiners in the camp. It may seem strange, but it is nevertheless true, that the line officers appreciated the value of those examinations more readily than the medical officers. The line officer judged his men in terms of conduct, behavior, and efficiency which, after all, is equivalent to the standards of the neuropsychiatric examiner."[31] That this number of neuropsychiatric casualties has been a tremendous expense to the government is well rea-

lized.[30,31,65,110,136] In the 17 years from 1923 to 1940 the Veterans Administration paid out $641,857,704 to claimants having disabilities of the nervous system, and from 1926 to 1940 it expended for hospital treatment of beneficiaries with disorders of the nervous system the sum of $282,679,909.[30] Thus about one billion dollars has been spent for the care of the neuropsychiatrically ill veteran of World War I.[30,65] In the one fiscal year ending June 30, 1940, nearly 22 years after the Armistice, the government paid out in compensation to neuropsychiatric cases $41,889,360 to 68,727 men, of whom 35,846 were diagnosed as psychoneurosis or neurosis.[136] The average hospitalized, "service-connected," neuropsychiatric patient cost the government about $30,000 during his lifetime.[138] Almost three-fifths of the beds in our 79 Veterans Hospitals were, up to the present war, occupied by neuropsychiatric cases.[30,65,136] Of the 90 so-called "facilities" of the Veterans Administration which as of June 30, 1940, were in operation over the country, 27 were hospitals adapted for neuropsychiatric cases, chiefly psychoses. On that date there were 33,016 such patients in those 27 hospitals, more than one-half of the total hospital population of the Veterans Administration.[30] Further, the hospital turnover of psychotic patients is much slower than that of the general medical and surgical, or even tuberculous patients.[30] It is said that neuropsychiatric casualties are 16 times more apt to result in permanent disabilities than are any other types of illness.[180] In the first World War, over 20 soldiers out of every 1000 were discovered in our army to have some form of mental illness,[127] and while in the last draft of World War I, approximately 2% of all candidates were excluded because of some neuropsychiatric disorder, an additional 3% were later discharged because they were found to be suffering from some type of neuropsychiatric disorder. In our A. E. F. the casualties due to nervous and mental disease were 9.5 per 1000.[60] There is a tabulation in the official history which gives a total of 69,394 rejections, because of disorders of the nervous system, as of May 1, 1919, and of this total, there were:

Mental deficiency	31%
Neuroses	17%
Psychoses	11%
Organic nervous diseases and injuries	10%
Epilepsy	9%
Constitutional psychopathic state	9%
Endocrinopathies	7%
Drug addiction and alcoholism	6%

However, the existence of neuropsychiatric problems was not limited to the United States Army alone, but was also important in the German Army,[53,118] where 5% of the base hospital beds were kept for neuropsychiatric casualties.[28] Almost immediately after 1918, there was begun a psychological organization of the German Army and people for war, leading to the establishment in 1929 of a Psychological Laboratory by the German Army.[58] Of the British casualties of World War I, those from neuroses were 34 per 1000; and in 1918, of 160,000 men drawing pensions, 20% were suffering from functional nervous and mental disorder,[31] and of 180,496 Canadian casualties of World War I, 24 per 1000 were nervous and mental diseases.[31]

From a more detailed study of these neuropsychiatric casualties of World War I two important factors can be discovered regarding the onset of their difficulties. The first is this: most of the men had manifested characteristic symptoms previous to their military service. From the data

TABLE 1. INCIDENCE OF POSITIVE SOCIAL HISTORY DATA IN NEUROPSYCHIATRIC CASUALTIES

Social history data	Simon.[16] Study of 38 cases (%)	Simon and Hagan,[17] Study of 400 neuropsychiatric casualties of which 200 are Army and 200 are Navy and Marine Corps (%)	Simon and Hagan,[17] Study of 175 neuropsychiatric rejectees under Selective Service System (%)	Simon, Hagan and Hull,[18] Study of 183 neuropsychiatric patients (%)	Rosenberg and Lambert,[18] Study of 200 cases (%)	Billings et al,[19] Study of 200 cases. Per cent by which patient exceeded controls
Previous hospitalization for mental illness or previous treatment by a psychiatrist	26.3	Army—27.5 Navy—22.5		Army—20.9 Total—10.3	6 0	
Had come from "broken home"	44.0	42.5	28.5	37.3		10
Had psychoses in immediate family group		35.2	18.0	33.9	19 0	32
Previous antisocial behavior	18.1	12.7	15.4	8.3		45
Poor adjustment in school						36
History of excessive alcoholism		10.4	18.8	19.4	Rare	
Poor occupational adjustment	44.0				54.0	52
Onset of patient's disability within 1 month or less of army service		19.5		10 0	44.5	
Onset of patient's disability within 6 months or less of army service		58.5		42 0	97 0	95

available on 50,042 neuropsychiatric patients it was seen that for 84%
of them the average time of onset of their symptoms was 5 years before
entering the service.[127] Of the psychotic, there was evidence of illness
preceding enrollment in 87%.[31,127] Of the psychoneuroses, 95% had had
symptoms prior to entering military service.[31,127] In 97.5% of the epilep-
tics there was evidence of the disorder for 1 year or more before service.[31,127]
In 99% of the cases of drug addiction or alcoholism there was a definite
history preceding service, and in all cases in which data were available, a
history of alcoholism for more than 5 years before entering service was
ascertained.[127] The second important point is: there were significant
family histories in the majority of the neuropsychiatric casualties. Of the
psychoses, more than 50% had a "positive" family history,[31] of the psycho-
neuroses, 55.7% had a family history of "neurotic taint."[31] Of the cases
of "war neurosis" in the A. E. F. of World War I, there was a history of
neuropathic makeup or "neuropathic stock" in 40%.[127]

II. The Examination and Selection of Men for the Armed Forces.
Turning from the patients of World War I to contemporary cases, we find
that the problem of neuropsychiatric casualties is one of equally great or
even greater magnitude. Of the men recently returned to Canada from
the theater of war in the Low Countries, over 30% were disabled by con-
ditions of the nervous system.[31] Disability resulting from mental dis-
orders is of more frequent occurrence than from any other cause with the
exception of actual injury suffered in combat.[82] Up to September 1, 1942,
there were 8145 discharges from our armed forces for mental illness.[82]
About one-third of the medical discharges are neuropsychiatric.[80b] Tuber-
culosis, which is next in number of discharges, is responsible for 1281 cases
during the same period.[82] And in these cases of mental illness, these same
two factors of predisposition and background continue to be important;
hence the importance of an adequate social history on every prospective
service man becomes increasingly evident.[3,34,42,114,122,163,169] Gowan[65] esti-
mates that one-half to two-thirds of those suffering mental or nervous
disturbances among our armed forces show definite predisposition, while
Gray[67] says that about 80% of the severe cases of nervous illness in military
hospitals have previously shown emotional instability. The value of
social data is further revealed by the studies done by Simon and his asso-
ciates[166,167] and by Sullivan,[181] from which the comparison shown in Table 1
was taken. Further, Simon[167] goes on to state that if five objective social
factors (previous mental illness, broken home, psychosis in immediate
family, arrests, and alcoholism) are studied in a group of military per-
sonnel who became psychotic, 72.2% of them have one or more factors
present and over 12% have three to five of them. And Lewis[105] who
investigated 300 neuropsychiatric casualties found certain traits which
were present with significantly greater frequency in the histories of men
who had proved unsuitable for military duty; these were: (1) History of
mental disturbance, including neurosis, in parents or siblings. (2) Unsatis-
factory work record prior to enlistment. (3) Psychopathic traits of
personality. (4) Symptoms of present illness before enlistment.

Further, other papers which stress the positive correlation which exists
between success in the services and the man's background are numer-
ous.[3,14,20,21,26,28,86,129,135,153,187] It has also been shown that of the soldiers
who break down in *active* duty because of a personality disorder, there is a
high incidence of significant factors in their past history. This has been
borne out by numerous reports (Table 2).

Without question, it is at the time of the Local Draft Board examination

and especially at the Induction Center examination that psychiatry can play an extremely important rôle in our war effort, for the fundamental truth remains that in a fighting force the elimination of the unsuitable man—and he is more often unsuitable for temperamental reasons than by intellectual defect—at the earliest possible stage is all important.[57,101] The estimates as to the percentage of men who later break down in military service and who could have been discovered by an adequate neuropsychiatric examination at the time of induction vary from 39%[34] to 50%,[57] to 75%.[96] It is significant that of 69,394 neuropsychiatric casualties of World War I, 40.1% of them were discovered during the routine examination of all men on their arrival at a mobilization camp.[127] At the present time the percentage of neuropsychiatric rejections varies according to examiner and locality, as is suggested by Table 3.

TABLE 2.—INCIDENCE OF SIGNIFICANT FACTORS IN PAST HISTORY OF SOLDIERS WHO BREAK DOWN AFTER ACTIVE DUTY

Factors	Love[105] 174 cases (%)	Cooper[33] 207 cases (%)	Hadfield[75] 332 cases (%)	Gillespie[57] 56 cases (%)	Sutherland[185] 100 cases (%)	Brill[22] 200 cases (%)	Wolfson[204] 100 cases (%)
Previous episode of personality disorder	34.2	23	32	..	36		
Previous history of concussion or fractured skull	3.8	17					
Had come from "broken home"				31			
Previous antisocial behavior				.		17	
Other significant factors in past history	53.0			.	11	60	
"Inferior" previous personality	.	58	28	..	33	..	72
Family history reveals "poor mental or economic status"	.	50		62	..	50	14

TABLE 3.—PERCENTAGE OF SELECTEES REJECTED FOR NEUROPSYCHIATRIC REASONS

Type of examination	Selectees rejected for neuropsychiatric reasons (%)	Date of article	Bibliography reference
Massachusetts Local Boards	9.0	May,	195 and 196
Massachusetts Induction Centers	2.0	June 1941	
New Jersey Induction Centers	20.0	May 1941	154
Boston Induction Center	7.4	Aug. 1941	70
Indiana Induction Center	4.2	April 1941	125
Minnesota Induction Center	2.5	Nov. 1941	4
Mississippi Induction Center	Wh.—11.6 Col.—12.4 (venereal disease omitted from percentage)	Jan. 1942	161
Entire Country, Local Boards	6.0	Jan. 1942	139
Massachusetts Local Boards	5.04	April 1942	35
Virginia and District of Columbia Examining Centers	32.1	Aug. 1942	77
Boston Induction Center	7.5	July 1942	18
Rhode Island Naval Training Station	4.0	Nov. 1942	203
Florida Induction Center	1.92	Nov. 1942	20
Virginia and District of Columbia Examining Centers	30.7	Nov. 1942	77
Washington, D. C., Selective Service	22.2 (includes educational rejections)	Nov. 1942	167
All Corps Areas, U. S. Army Induction Center	3.13 (Nov. 1940 to Dec. 1941) 8.01—wh.—from May 1942 to Sept. 1942 15.49—col—from May 1942 to Sept. 1942 (venereal disease rejections omitted from the percentage. Includes educational rejects)	Jan. 1943	156
All Corps Areas, U. S. Army Induction Center	7.5	May 1943	80b

In 5 of the articles the percentage of all *rejectees* that were rejected for neuropsychiatric reasons was stated as shown in Table 4; in 3 of the articles of the total number of men seen, the neuropsychiatric rejections were divided as shown in Table 5.

TABLE 4.—PERCENTAGE OF REJECTEES REJECTED FOR NEUROPSYCHIATRIC REASONS

Type of examination	Rejectees rejected for neuropsychiatric reasons (including illiteracy) (%)	Date of article	Bibliography reference
Massachusetts Local Board . . .	15.0	May, June 1941	195 and 196
Massachusetts Induction Center	25.0	June 1941	
Massachusetts Induction Center	24.4	April 1942	35
Florida Induction Center . . .	10.62	Nov. 1942	50
All Corps Areas, U. S. Army Induction Centers	23.9—wh.—from May to Sept. 1942 34.7—col.—from May to Sept., 1942 (venereal disease rejections omitted from the percentage)	Jan. 1943	198

TABLE 5.—PERCENTAGE OF SELECTEES REJECTED, ACCORDING TO TYPE OF NEUROPSYCHIATRIC DISORDER

Type of mental illness	Total men examined (%)		
	Green[70] Aug. 1941 799 cases	Hadley[76] Aug. 1942 1750 cases	Hadley[77] Nov. 1942 2500 cases
1. Mental deficiency	0.96	3.44	2.8
2. Psychopathic personality	1.6	1.6	1.56
3. Major abnormalities of mood	0.23	0.22	0.2
4. Psychoneurosis	1.43	10.0	10.6
5. Schizoid and related personality	0.5	11.48	11.6
6. Chronic inebriety	0.5	1.94	2.4
7. Syphilis of the CNS	0.23		
8. Other organic diseases of brain, spinal cord or nerves . .	1.31	3.42	3.8

In 4 of the articles, of the total neuropsychiatric rejections, the types of mental illness were divided as shown in Table 6.

TABLE 6.—PERCENTAGE AS TO THE TYPE OF NEUROPSYCHIATRIC DISORDER IN NEUROPSYCHIATRIC REJECTEES

Type of mental illness	Neuropsychiatric rejections (%)				
	Currier[35] April 1942 87 cases	Wittson et al.[203] Nov. 1942 600 cases	Aita[4] Nov. 1941 242 cases	von Storch[195] May 1941 209 cases	Simon and Hagan[167] Nov. 1942 175 cases
1. Mental deficiency	16.01	37.0	38.0	16.2	15.4
2. Psychopathic personality	14.9	26.0	5.8	14.3	8.6
3. Major abnormalities of mood . . .	2.3	..	5.4	2.8	3.4
4. Psychoneurosis	49.4	8.0	17.3	27.2	37.7
5. Schizoid and related personality . . .	9.1	"psychoses" 4.0	11.5	8.1	18.9
6. Chronic inebriety	3 5	..	2.5	5.7	7.4
7. Syphilis of the CNS	0.0	..	0.0	0.0	1.2
8. Other organic diseases of brain, spinal cord or nerves	11.0	24.0	18.6	16.9	7.4

There has been a considerable number of articles dealing with the necessity for a psychiatric examination on all recruits and the problems associated with such a brief examination. Further, these problems of rejection, examination time, privacy, and load per examiner have been well summarized in the War Department pamphlet entitled "Mobilization Regulations 1–9" and in recent directives from the Surgeons-General Office.[8] There are articles pertaining especially to selection to the Air Corps,[14,68,69,129] and for the Navy,[41,54,72,83,85,179,186,187] but most of the articles relate to the general selection for any armed service. A few of the articles deal with the problems of an advisory board psychiatrist for the Local Draft Boards.[122,124,181] The majority of the articles recognize the importance of past interpersonal relationships in predicting the adjustment a selectee will make to army life but it is particularly stressed in some.[20,26,28,44,138] It is well realized that army service should be regarded as a vocation for

which not every man with a good physique is suitable and the fundamental problem is the creation of a fighting force best equipped to win.[143,144]

Billings et al.[155] have suggested 9 signs which suggest maladjustment and personality disorder in the prospective soldier: hypochondriasis before entering the army; excessive generalized sweating (with associated signs of autonomic instability); irregular work record; under-activity; disturbed sex development (excluding moderate delays in maturation); difficulty in making friends; two or more morbid fears; no definite ambition or definite ambition and accomplishment; and volunteering for service through regular channels, Selective Service or National Guard.

There are three types of persons who should not be inducted into such a fighting force: first, those whose capability for self-support and whose utility would be destroyed or gravely reduced by army service; second, those who would develop psychotic or psychoneurotic illness in such service; third, those who will do well in the Army but who cannot be discharged back to civil life without serious disturbance of personality.[151] These above points of view have been further developed in many other articles.[3,9,35,61,97,100,110,153,160,183,193]

In a discussion of the technique of the neuropsychiatric examination at an induction center, most articles agree that a 5 minute examination should be minimal and that up to 15 minutes should be allowed if deemed advisable.[4,50,164,178,182] A few papers mention that examinations are now sometimes done in as little as 2 to 3 minutes.[50,164] At some induction centers, a policy which has proven of value is the use of a 3 to 10 minute original examination with the privilege of a somewhat longer check examination later for doubtful selectees.[93] There have been many helpful papers suggesting forms for brief neuropsychiatric examination.[14,92,99,121,123,105] Other articles have dealt more particularly with one clinical type and have given primary and more detailed consideration to that clinical type as follows: (1) Mental deficiency;[36,45,46,71,150,197] (2) Psychopathic personality;[10,11,12,25,41,42,72,78,103,111,120,132,140] (3) Major abnormalities of mood;[25] (4) Psychoneurosis;[35,95,99,132,171] (5) Schizoid and related personality;[25,192] (6) Chronic inebriety;[130] (7) Syphilis of the Central Nervous System;[126] (8) Other organic nervous diseases of brain, spinal cord, nerves.[33,102,126,165]

Further, some papers contain a brief description of all the clinical types of rejectable personality disorders.[4,19,84,85,92,94,117,136,142,154,172,182,184]

Numerous papers have been written on the general procedure and technique of the induction center examination.[18,23,27,62,73,93,96,123,148,177] The minimal psychiatric examination seeks to bring out, as far as the individual's truthfulness will permit, certain points in his life history which are important as indications of the abnormal or disordered personality,[7] and hence there are certain types of persons that will sometimes be missed at the induction examination;[99] these are: (1) Some alcoholics and other addicts; (2) mild manic-depressive persons, especially if in a latent phase; (3) overt but undetected homosexuality (it is estimated that as high as 2% of the adult male population is frankly homosexual[159]); (4) psychopathic personalities; (5) some cases of hysteria (those who love excitement and are at their best in the examination); (6) early schizophrenia with a good façade; (7) certain types of organic disease of the nervous system, as some epileptics, latent central nervous system syphilis.

In order to uncover these above types, adequate life history data must be available.

III. Psychiatric Problems of the Armed Forces. The problem of the recognition, prevention and treatment of personality disorders in soldiers

has resulted in a considerable number of articles. The steps through which the average recruit passes in his army career are essentially five: first, the examination by his local Selective Service Board; second, the examination at the Army Induction Center (approximately 1 day); third, the reception center (7 to 10 day period); fourth, the replacement training center (usually a period of 2 to 3 months); fifth, the tactical unit.[180] In any of these five stages a personality disorder may become manifest and there is occasional opportunity for disposition and treatment.

Some authors suggest that the primary functions of military psychiatry are diagnosis and the exclusion of undesirable persons from service as rapidly as possible.[49,85] The mission of the Medical Corps is the conservation of manpower and the preservation of the military forces; its hospital facilities must be utilized to restore soldiers speedily to health and fighting efficiency and cannot be burdened with cases requiring prolonged care; thus, while a certain amount of temporary therapy is and should be applied, the main objective is to direct the more serious mental disorders back to community care.[80,145,146] Courses in military neuropsychiatry are now being given to the Medical Corps and there seems to be adequate psychiatric awareness in military medicine.[17,21,47,79] In 1940 the Army admission rate for psychoses was 6.13 per 1000 population[145] while the civilian rate in 1935 for the age group of 20 to 29 in New York and Massachusetts was 3.44 per 1000 population.[39] This same awareness of the importance of psychiatry exists with both our Allies[131] and our enemies.[59,134] Most papers state that the underlying personality of the individual soldier developing the functional nervous disorder is the etiologic agent, rather than military service *per se*, but military service does furnish an excellent medium for the growth and development of mental illness in susceptible personalities.[94,140,169,176,188] It is suggested in some articles that there are perhaps two chief types of mental reactions which appear peculiar to military service: first, the acute war neurosis;[156] second, the acute schizophrenic reaction which is explosive in onset and clears rapidly when the conflict situation is cleared.[43,145] The similarity between civilian mental illness and mental illness of soldiers was also noted in World War I, during which no really new forms of mental disorder were seen.[53] During World War I, in 1918, the discharge rate for mental and nervous disorders was approximately 0.7 per 100 strength while the latest figures for this war show the rate to be about 0.4 per 100, and the hospital admission rate of neuropsychiatric casualties did not greatly exceed 2.7 per 100 admissions *per annum* in 1942 and recently these admissions were only 2.5% of the admissions for all causes; although about 5.4% of all patients remaining in Army hospitals are neuropsychiatric.[80b] The following table is a summary of the various types of mental illness occurring in the armed forces and the relative percentage of each type as given by various articles (Table 7).

The symptoms which the patients develop under the stress of training or combat are the result of conflicts which are chiefly between self-preservation and the ideas of duty and self-respect. During the training period this conflict can be solved by a variety of means, sometimes not laudable from the standpoint of morale—by reporting sick, by seeking a soft job, by "gold-bricking," and many others.[21] In soldiers during the training period, some increase in anxiety and tension under war conditions is inevitable. If, however, this anxiety incapacitates an individual then it is most probably not associated with the war but represents a personal problem.[194] The psychologic hazards which may precipitate a personality disorder

TABLE 7 — TYPES OF NEUROPSYCHIATRIC ILLNESS DEVELOPING IN ARMED FORCES

	Mental deficiency	Organic diseases of nervous system	Chronic addiction	Constitutional (a) psychopathic states	Total per cent of all psychoses	Major abnormalities of mood	Schizophrenic reaction type	Paranoid states	Total per cent of all psychoneuroses	Anxiety state	Hysteria	Hypochondriasis	Neurasthenia (and neurocirculatory asthenia)	Reactive depression	Obsessive states	Other psychoneuroses	Malingering
World War I, cases from over sea service	9.15	5.0*	0.7	4.65	13.2				31.8								
World War I, total cases	13.1	8*		5.3	12.2		6.4	0.6	7.8	70.0	6.2		12.6			10	
World War I, only neuroses considered	1.8	3.0		‡	1.3	0.5	1.7			80.7	20.0	2.4					8 2
				35.0	41.0		1.9	0.9		64.0	10.3			43	8	8	
No neurologic cases included in percentage	5.1			2.3	2.3		11.1		82.0	45.2	16.0						
No neurologic cases included in percentage				30.0	12.8	0.9	8		83.0	‡	50.0	Some					
Only neuroses included in percentage					37.0	5.0		1.5		‡	Some	Some			8		
	4.0			18.0			1.0			53.0	24.0		11.0	12		2	
Only neuroses considered		17.0*			30.5		81.0		52.5	31.0	11.0	0.4	11.0	23	2	2	8
										44.0	25.0	10.0	24.0	3	2	16	2
										11.0	17.0		8.0				

* Highest   † Not common   ‡ Most of the neuroses   § Most of the psychoses

during the training period have been discussed in some articles[37,113] but they are particularly well handled in the articles by Knight and Orr,[99] by Billings,[15] and by Pignataro.[141] These precipitating factors during the training period, together with the articles dealing with them, are:

1. Separation from home ties.[14,64,80,88,99,123,142,172,185]
2. Anxiety over home responsibilities and family.[80,88,112,172]
3. Change in habit routines.[20,21,80,88,123,142,172]
4. Necessity of submission to authority and discipline.[20,42,66,80,85,123,142,172]
5. Loss of prestige and other "narcissistic" blows.[99,112,172]
6. Contacts with other men without any privacy, which may:
   (a) Arouse antagonism.[29,99]
   (b) Arouse homosexual anxiety.
7. Stirring up more aggression than the man can handle and guilt over such aggressions.[20,142,172]
8. Exhaustion and monotony.[1,20,21,56,88,99,112,145,169,172,191]
9. Sex deprivation and sex conflicts.[99]
10. Arousing fears of bodily injury or death.[56,88,123,172]

According to most authors, the neuropsychiatric disabilities occurring in active military service in combat also result from the conflict between acquired social attitudes and the "instinct" of self-preservation. However, to be adequate and to fulfill the purpose of protection for which it is psychologically designed, the neurosis must protect both the soldier's ego and his physical being—that is, it must permit him to escape from the intolerable situation created by the impending dangers and also to accomplish this without loss of self-respect.[189,190] Every neurotic illness is a result of the reaction of an individual to his environment; the predisposition of the patient playing the predominant rôle and the immediate environment, the precipitating one.[75,170] In the psychoanalytical literature, the homosexual-narcissistic libido structure of potential war neurotics is emphasized as the basis of their vulnerability,[199] but other investigators view the chief neurotic mechanisms as defensive or automatic self-preservative drives.[112] The precipitating factors present during the combat zone are well discussed in many articles[15,200,206] and can be summarized, together with the papers dealing with them, as follows: (1) All of the factors of the training period.[185,202] (2) Fear of his own cowardice.[169,185,200] (3) Conflict between self-preservation and group loyalty, with sacrifice for an ideal.[87,202] (4) Disappointments and feelings of frustration.[13,202,206] (5) Increased fatigue and increased responsibility.[13,112,170] (6) Poor food and poor sanitation.[13] (7) Exposure to explosions, blast, and gases.[7,74,109,133] (8) Effect of climate, and of arctic or tropical diseases.[115]

The general principles and the specific measures of treatment for the personality disorders occurring in military service are well summarized by Billings.[15] The treatment of such disorders in the training camp period is dealt with in several articles[99,108,152,180] and particularly well handled in articles by Stilwell and Schreiber,[180] and by Garmany.[52] The general management of the treatment in the combat zone is discussed in many papers[40,90,128,159,206] and is especially well considered in papers by Aiken;[2] Smith;[172] and by Altman, Pillersdorf, and Ross.[5] This last-mentioned paper has a good discussion of the personality factors which would interfere with successful treatment; as does also the paper by Lewis and Slater.[105] Further suggestions and regulations regarding the management of a neuropsychiatric service are contained in many military publications.[8]

The important factors in the treatment of personality disorders *in the training camp period*, as summarized in the literature are:

1. *Prophylactic treatment:* (a) Establishment of good morale.[15,52,99,105,180] (b) Elimination of manifest personality disorders.[15,51,52,54,108,141,206] (c) Avoidance of monotony.[15,52,99]

2. *Active treatment:* (a) Discharge to civilian life.[15,52,54,64,145,180] (b) Modification of type of service.[15,51,52,95,141,180] (c) Use of labor battalions.[34,42,51,52] (d) Psychotherapy (discussed under "combat zone").

The methods of treatment of psychiatric problems, used somewhat in the training period, but especially pertaining *to the combat zone*, together with the articles which deal with the method listed, are:

1. *Prophylactic treatment:*[2,5,40,90,125,159,172,191,206] (a) Establishment of group morale. (b) Personal interest in men by officers. (c) Avoidance of fatigue. (d) Group talks: explanation of war motives, of fear, etc. (e) Careful watch for prodromal signs. (f) Transfer to other duty.[34] (g) Removal from combat zone.[101]

2. *Active treatment:*[2,5,40,90,125,159,172,206] (a) Importance of restoring good physical condition, particularly if confusion, excitement and loss of memory are prominent symptoms.[7,13,22,87,99,101,108,109,159,170,199,200,206] (b) Psychotherapeutic measures: (1) Thorough history taken.[32,146,199] (2) Immediate treatment.[6,13,60,87,99,107,109,112,189,190,199,206] (3) Reassurance, persuasion suggestion.[13,22,75,101,108,109,185,189,199,206] (4) Reliving and recalling the traumatic experience with the expression of the underlying fears; hypnosis and sedative drugs used if needed.[6,13,39,40,56,75,116,146,155,159,169,185,200] (5) Dealing with the secondary gains present in the illness.[5,99,106,107] (6) Base hospital used only if necessary for psychoses and severe neuroses.[99,172] (7) Insulin therapy.[40,157,159,199] (8) Convulsive therapy.[63,146,159,185] (9) Reëducation.[22,32,60,159] (10) Occupational and physical therapy.[32,40,48,87,158,201] (11) Analysis.[13,185] (12) Group psychotherapeutic procedures.[5,16,89,173]

The efficacy of such measures of therapy can be judged somewhat by disposition of psychiatric patients in the armed forces, and this has been summarized in Table 8. Further, as to casualties from certain overseas areas, about 15% to 20% of those reaching this country are neuropsychiatric, but it should be noted that the actual ratio of neuropsychiatric disorders to all casualties has been about 5% in those areas.[805]

TABLE 8.—DISPOSITION OF PSYCHIATRIC CASUALTIES IN THE ARMED FORCES

Type of personality disorder	Bibliography reference	Returned to unit		Placed in base hospital (%)	Returned for limited duty (%)	Not sufficient improvement to return to any duty (%)
		Without leaving combat zone (%)	After treatment at base hospital (%)			
All psychoneuroses	127*	65.0				
	127*		60			
	34		33			67
	32	38.0	23		23	12
	75		15		43	42
	185		9		19	72
	190*	65			20	5
Hysteria	32*	63.5				
	108		44.4	55.6		
	22	50.0	27		20	7
Anxiety states	18	55.8		44.2		
	32	55			20	16
Personality disorder associated with organic disease	18	58.3		41.7		
Psychoses	108	100		100		

* World War I

IV. Rehabilitation of Psychiatric Casualties. When one considers the importance of the problem, it is surprising how few articles have been written about the psychiatric problems associated with the registrant rejected by the armed forces or the readjustment of the man discharged from military service because of a personality disorder. The return of these men to civilian life can give rise to personality problems in the men themselves and create psychiatric difficulties for the communities.

There are many competent men in civilian life who are adjusting well but who do not have the qualities desirable for good soldiers, and it must be emphasized that no stigma be placed on the rejected candidates and that civilian morale is not unfavorably affected in carrying out the rejection of unsuitable candidates.[20] It is important to emphasize constantly that the Selective Service is a draft of total manpower for the purpose of determining for what duties a man is best fitted, army or civilian.[20] The problems which arise in a rejected man are, first, reactions to the fact of being rejected, for whatever reason; and, second, reactions to the specific reason for rejection.[137] The protection of the rejected man depends first upon the manner in which he is informed of the reasons for rejection, second, upon the giving of suggestions as to where treatment can be obtained if it is needed, and third, on the considerate interpretation of the rejection to the registrant's family and his community.[136] The Surgeon-General has recognized these needs in a recent circular letter.[8] The Illinois Psychiatric Society has arranged with the Army Induction Boards to furnish rejected selectees with free psychiatric advice, vocational guidance, and social aid in order to facilitate their return to a useful life.[151] Further, in order that the registrant can know for sure if he will be inducted before he winds up his affairs and bids farewell to family and friends, Pennsylvania holds Local Board and Induction Board examination at about the same time but postpones actual induction into military service for 2 or 3 weeks.[137] In Pennsylvania cases of nervous and mental disorders are referred following rejection to the State Department of Welfare and cases of venereal disease to the State Board of Health; further, the Public Charities Association was willing to advise the rejected registrant and refer him to the proper social agencies best fitted to assist him.[137] One survey, made in Michigan, consisted of follow-up letters to the local boards asking about the occupational status of 3500 rejected registrants and showed that before the Army examination 84 % had been employed, mostly in unskilled occupations, and 16 % had been unemployed; after rejection, 72% of the men regained their former employment, and 3 % found new jobs, and of the remaining 25 % some were unemployed, some in school, and some unaccounted for.[137]

The problems of a soldier discharged from the military service are somewhat different. His problems are mainly:[147,149] (1) To find a means of economic support. (2) To find acceptable civilian sublimations for the aggressiveness released and encouraged by a belligerent war psychology. (3) To assume the ordinary relationship responsibilities of adult life. (4) To accept the need for independence, initiative, self-management, and self-discipline in an environment which no longer gives him security.

The compensation, pension, and post-war reward systems inaugurated after World War I hampered the morale of the dismissed soldier by encouraging him to believe that he had the right to be dependent on the government indefinitely.[81,119] The problem of a proper rehabilitation program in these persons has been considered by Solomon[174] and has been well discussed in the articles by Sommer and Weinberg[175] and by Preston.[149]

Further Schuyler,[162] and others[24,54] discuss the ways in which a hospital psychiatric social worker may aid in the readjustment of a man discharged from the Army because of personality defect. The importance of the problem of rehabilitation is shown by the fact that of the total of 2354 veterans returned to their homes in Illinois by the military service, 40% had neuropsychiatric or personality defects.[175] The homes of 75 of these veterans were visited and the employment situation was found to be:[175] 13.1% idle, 63.1% employed, 5.2% in vocation schools, and 18.4% had reëntered military service.

The statistics from World War I concerning post-war adjustment in 758 discharged neuropsychiatric cases are shown in Table 9.[127] In view of the enormity of this problem of rehabilitation it would seem advisable that further investigation be carried out on the rejected registrant and the discharged soldier who suffer from personality disorder.

TABLE 9.—POST-WAR ADJUSTMENT OF NEUROPSYCHIATRIC CASUALTIES OF WORLD WAR I

| Type of patient | Year of survey | Carrying on in civilian life | | In hospital or having other difficulty (%) |
		Normal (%)	"Neurotic" (%)	
Men in Class A	1919–1920	45 2	22.9	
Men in Class A	1924–1925	40 7	42 3	
Men of Base Hosp. 117	1919–1920	61 0		39
Men of Base Hosp. 117	1924–1925	80 8		

REFERENCES

(1.) Adams, J. C.: U. S. Nav. Med. Bull., 39, 514, 1941. (2.) Aiken, M. H.: New Zealand Med. J., 40, 345, 1941. (3.) Aita, J. A.: Proc. Staff Meet. Mayo Clin., 16, 283, 294, 305, 1941. (4.) Aita, J. A.: War Med., 1, 769, 1941. (5.) Altman, L. L., Pillersdorf, L., and Ross, A. T.: War Med., 2, 551, 1942. (6.) Altman, L. L.: War Med., 3, 267, 1943. (7.) Anderson, E. W.: J. Ment. Sci., 88, 328, 1942. (8.) Army Regulations: A.R. 35-1440, A.R. 40-1025 (par. 18), A.R. 600-500, A.R. 600-505, A.R. 615-360, A.R. 40-100, A.R. 40-105, A.R. 40-110, M.R. 1-9; Selective Service Medical Circular No. 1; Manual for Courts-Martial, U. S. Army, 1928 (pars. 30c, 35c and 63); T.M. S-260 W.D. 1941—Fixed Hospitals of the Medical Department; T.M. S-320 W.D. 1941—Psychology and Aviation Medicine; T.M. S-325 W.D. 1940—Neuropsychiatry and Aviation Medicine; Circular Letters, S.G.O. 1941, Nos. 10, 12, 19, 24, 42, 18, 64; Circular Letter No. 66, W.D. 1941; Hospital Regulations 40-40 (Neuropsychiatric Section); Ulio, J. A.: Memorandum from Sec. of War, J. Am. Med. Assn., 121, 1095, 1943. (9.) Boganz, C. N.: Mil. Surg., 86, 471, 1940. (10.) Boganz, C. N.: J. Crim. Psychopath., 4, 459, 1943. (11.) Boganz, C. N.: Dis. Nerv. Syst., 4, 82, 1943. (12.) Bsille, W.: Am. J. Psychiat., 97, 753, 1941. (13.) Bennet, E. A.: Med. presse, 205, 128, 1941. (14.) Bigelow, R. B.: War Med., 2, 381, 1942. (15.) (a) Billings, E. G.: Army Med. Bull., No. 58, p. 1, Oct., 1941. (b) Billings, E. G., Ebaugh, F. G., Morgan, D. W., O'Kelly, L. I., Short, G. B., and Golding, F. C.: Analysis of 100 Army Psychiatric Cases and 100 Enlisted Men. (To be published in War Med.) (16.) Blair, D.: Lancet, 1, 204, 1943. (17.) Blakeslee, G. A.: Bull. New York Acad. Med., 18, 775, 1942. (18.) Bloomberg, W., and Hyde, R. W.: Am. J. Psychiat., 99, 23, 1942. (19.) Boshes, B.: Illinois Med. J., 82, 361, 1942. (20.) Bowman, K. M.: War Med., 1, 213, 1941. (21.) Brill, N. Q.: J. Lab. and Clin. Med., 28, 189, 1943. (22.) Brill, N. Q.: Mil. Surg., 90, 590, 1942. (23.) Brussel, J. A.: J. Med. Soc. New Jersey, 39, 442, 1942. (24.) Brussel, J. A., and Wolpert, H. R.: War Med., 3, 139, 1943. (25.) Bullard, D. M.: Psychiatry, 4, 231, 1941.

(26.) Campbell, C. M.: J. Am. Med. Assn., 116, 1883, 1941. (27.) Campbell, J. D.: Kentucky Med. J., 39, 110, 1941. (28.) Cohen, L. H.: Connecticut State Med. J., 5, 453, 1941. (29.) Cohen, S. A.: War Med., 1, 205, 1941. (30.) Cooley, M.: Psychiatry, 4, 261, 1941. (31.) Cooley, M.: War Med., 1, 372, 1941. (32.) Cooper, E. L., and Sinclair, A. J. M.: Med. J. Australia, 2, 73, 1942. (33.) Crank, H., and Robbins, L. L.: Bull. Menn. Clin., 5, 171, 1941. (34.) Curran, D., and Mallison, W. P.: Lancet, 2, 755, 1940. (35.) Currier, D. E.: J. Maine Med. Assn., 33, 65, 1942.

(35.) Davidson, H. A.: Mil. Surg., 86, 477, 1940. (37.) Davidson, S. M.: New York State J. Med., 42, 1654, 1942. (38.) Dawson, W. S.: Med. J. Australia, 2, 375, 1941.

(39.) Dayton, N. A.: Med. Rec., 141, 476, 1935. (40.) Debenham, G., Hill, D., Sargant, W., and Slater, E.: Lancet, 1, 106, 1941. (41.) Dravo, E. L.: J. Indiana State Med. Assn., 33, 451, 1940. (42.) Dunn, W. H.: Psychiatry, 4, 251, 1941. (43.) Duval, A. M., and Hoffman, J. L.: War Med., 1, 854, 1941.

(44.) Ebaugh, F. G.: J. Am. Med. Assn., 117, 260, 1941. (45.) Esher, F. J. S.: Brit. Med. J., 2, 187, 1941. (46.) Esher, F. J. S.: Mental Health, 3, 14, 1942.

(47.) Farrell, M. J.: Military Laws and Regulations Pertaining to Disposition of Neuropsychiatric Cases, Collected Lectures of the Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including Military Psychiatry, p. 1, Metropolitan State Hospital, Waltham, Mass., 1942. (48.) Finn, N.: South African Med. J., 15, 483, 1941. (49.) Flicker, D. J.: Am. J. Psychiat., 98, 795, 1942. (50.) Flicker, D. J.: War Med., 2, 931, 1942. (51.) Freeman, R. G.: U. S. Nav. Med. Bull., 40, 631, 1942.

(52.) Garmany, G.: J. Roy. Nav. Med. Serv., 28, 160, 1942. (53.) Gaupp, R.: Deutsch. Militärarzt, 5, 358, 1940. (54.) Gerstle, M., Wagner, R. L., and Lodge, T.: U. S. Nav. Med. Bull., 61, 480, 1943. (55.) Gibbs, E. L., and Gibbs, F. A.: War Med., 2, 923, 1942. (56.) Gillespie, R. D.: Guy's Hosp. Gaz., 55, 38, 1941. (57.) Gillespie, R. D.: Psychological Effects of War on Citizen and Soldier, New York, Norton & Co., pp. 17, 207, 1942. (58.) Gillespie, R. D.: Brit. Med. J., 1, 445, 1942. (59.) Gitelson, M.: Dis. Nerv. Syst., 4, 125, 1943. (60.) Glueck, B.: Bull. New York Acad. Med., 18, 137, 1942. (61.) Goldstein, H. H.: Am. J. Psychiat., 99, 29, 1942. (62.) Goldstein, R.: Connecticut Med. J., 6, 522, 1942. (63.) Good, R.: J. Ment. Sci., 87, 409, 1941. (64.) Good, R.: Brit. Med. J., 2, 359, 1942. (65.) Gowan, L. R.: U. S. Nav. Med. Bull., 41, 129, 1943. (66.) Grant, N. W. D.: J. Lab. and Clin. Med., 28, 577, 1943. (67.) Gray, G. W.: Harper's Mag., 184, 630, 1942. (68.) Graybiel, A.: Some Problems in Aviation Medicine, Collected Lectures of the Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including Military Psychiatry, p. 227, Metropolitan State Hospital, Waltham, Mass., 1942. (69.) Graybiel, A.: J. Lab. and Clin. Med., 28, 590, 1943. (70.) Green, I.: Med. Rec., 154, 95, 1941. (71.) Greene, R. A.: Morons and Imbeciles of Draft Age, Collected Lectures of the Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including Military Psychiatry, p. 46, Metropolitan State Hospital, Waltham, Mass., 1942. (72.) Griswold, W. B.: U. S. Nav. Med. Bull., 40, 646, 1942. (73.) Grotjahn, M.: Dis. Nerv. Syst., 4, 85, 1943. (74.) de Gutierrez-Mahoney, W.: War Med., 1, 816, 1941.

(75.) Hadfield, J. A.: Brit. Med. J., 1, 281, 320, 1942. (76.) Hadley, E. E.: Psychiatry, 5, 371, 1942. (77.) Hadley, E. E.: Psychiatry, 5, 543, 1942. (78.) Hall, R. W.: War Med., 1, 372, 1941. (79.) Halloran, R. D., and Yakovlen, P. I.: Am. J. Psychiat., 99, 338, 1942. (80.) Halloran, R. D., and Farrell, M. J.: (a) Army Med. Bull., No. 65, p. 151, 1943; (b) The Function of Neuropsychiatry in the Army, read at the annual meeting of Am. Psychiat. Assn., Detroit, Mich., May, 1943. (81.) Hamill. R. G.: Dis. Nerv. Syst., 4, 86, 1943. (82.) Harris, T. H.: Dis. Nerv. Syst., 4, 69, 1943, (83.) Harrison, F. M.: War Med., 3, 113, 1943. (84.) Hecker, A. O., Plesset, M. R., and Grana, P. C.: Am. J. Psychiat., 99, 33, 1942. (85.) Helgesson, H.: U. S. Nav. Med. Bull., 40, 80, 1942. (86.) Holmes, C. D.: Kentucky Med. J., 40, 176, 1942. (87.) Hubert, W. H. deB.: Lancet, 1, 306, 1941. (88.) Hyland, H. H., and Richardson, J. C.: Canad. Med. Assn. J., 47, 432, 1942.

(89.) Jones, M.: Brit. Med. J., 2, 276, 1942. (90.) Jones, M., and Scarisbrick, R.: War Med., 2, 901, 1942. (91.) Jones, W. L.: Brit. Med. J., 2, 338, 1942.

(92.) Kahn, S.: Med. Rec., 155, 371, 1942. (93.) Kaplan, L. A.: Dis. Nerv. Syst., 4, 74, 1943. (94.) Kardiner, A.: War Med., 1, 219, 1941. (95.) Kelly, D. McG.: War Med., 3, 386, 1943. (96.) Kiene, H. E., Hassell, A. S., and Miller, A. S.: Am. J. Psychiat., 98, 509, 1942. (97.) King, H. N.: Med. Bull., 17, 387, 1941. (98.) Knight, R. P.: Bull. Menn. Clin., 5, 161, 1941. (99.) Knight, R. P., and Orr, D. W.: Bull. Menn. Clin., 5, 176, 1941. (100.) Koontz, A. R.: Hygeia, 20, 494, 1942.

(101.) Leigh, A. D.: Lancet, 1, 394, 1941. (102.) Lennox, W. G.: Fits and Paroxysmal Neuropsychiatric Syndromes in the Military Service, Collected Lectures of Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including Military Psychiatry, p. 89, Metropolitan State Hospital, Waltham, Mass., 1942. (103.) Lewinski, R. J.: U. S. Nav. Med. Bull., 41, 137, 1943. (104.) Lewis, A.: Quoted by Gillespie, R. D., Psychological Effects of War on Citizen and Soldier, New York, Norton & Co., p. 183, 1942. (105.) Lewis, A., and Slater, E.: Lancet, 1, 496, 1942. (106.) Lewy, E.: Bull. Menn. Clin., 5, 181, 1941. (107.) Lewy, E.: War Med., 1, 887, 1941. (108.) Love, H. R.: Med. J. Australia, 2, 137, 1942.

(109.) MacDonald, J. H.: Fear Neuroses, War and the Doctor, pp. 13, 1942. (110.) Madigan, P. S.: Psychiatry, 4, 225, 1941. (111.) Madigan, P. S., and Farrell, M. J.: J. Lab. and Clin. Med., 28, 485, 1943. (112.) Maskin, M.: Psychiatry, 4, 97, 1941. (113.) Mathers, A. T.: Canad. Med. Assn. J., 47, 103, 1942. (114.) McBee, M.: Am. J. Psychiat., 99, 431, 1942. (115.) McCartney, J. L.: War Med., 3, 351, 1943. (116.)

McLaughlin, F. L., and Millar, W. M.: Brit. Med. J., 2, 158, 1941. (117.) Medical Circular, Psychiatry, 4, 212, 1941. (118.) Meerloo, A. M.: Geneesk. gids., 18, 704, 1940. (119.) Menninger, K. A.: Bull. Menn. Clin., 5, 188, 1941. (120.) Menninger, K. A.: Bull. Menn. Clin., 5, 150, 1941. (121.) Menninger, W. C.: Bull. Menn., Clin., 5, 139, 1941. (122.) Menninger, W. C., and Greenwood, E. D.: Bull. Menn. Clin., 5, 134, 1941. (123.) Menninger, W. C.: War Med., 1, 843, 1941. (124.) Menninger, W. C.: J. Kansas Med. Soc., 42, 512, 1941. (125.) Mericle, E. W.: J. Indiana Med. Assn., 34, 410, 1941. (126.) Merritt, H. H.: Examination of Recruits: Detection of Commoner Neurologic Disorders in the Young Adults, Collected Lectures of the Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including Military Psychiatry, p. 23, Metropolitan State Hospital, Waltham, Mass., 1942. (127.) Michaelo, J. J.: War Med., 2, 172, 1942. (128.) Minski, L.: Med. Press, 205, 131, 1941. (129.) Mitchell, H. D.: Am. J. Psychiat., 99, 354, 1942. (130.) Moore, M.: Alcoholism and Drug Addiction in Military Service, Collected Lectures of the Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including Military Psychiatry, p. 60, Metropolitan State Hosp., Waltham, Mass., 1942. (131.) Myers, C. S.: Nature, 147, 564, 1941. (132.) Myerson, A.: Sexual Perverts; Constitutional Psychopaths, Hysteria, Malingerers, Collected Lectures of Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including Military Psychiatry, p. 74, Metropolitan State Hosp., Waltham, Mass., 1942. (133.) Neustatter, W. L.: Proc. Roy. Soc. Med., 35, 549, 1942. (134.) Notes and Comments, Lancet, 1, 311, 1942.

(135.) Oppenheimer, B. S.: Bull. New York Acad. Med., 18, 367, 1942. (136.) Orr, D. W.: Bull. Menn. Clin., 5, 131, 1941. (137.) Orr, D. W.: Bull. Menn. Clin., 5, 184, 1941. (138.) Overholser, W.: Am. J. Orthopsychiat., 11, 634, 1941. (139.) Overholser, W.: J. Assn. Am. Med. Coll., 17, 29, 1942.

(140.) Parsons, E. H.: J. Med. Assn. Georgia, 31, 324, 1942. (141.) Pignataro, F. P.: Mil. Surg., 90, 29, 1942. (142.) Porter, W. C.: War Med., 1, 364, 1941. (143.) Porter, W. C.: Am. J. Psychiat., 98, 317, 1941. (144.) Porter, W. C.: War Med., 2, 543, 1942. (145.) Porter, W. C.: Psychiatry, 5, 321, 1942. (146.) Porter, W. C., Novak, J. G., and Lemkau, P. V.: Mil. Surg., 92, 372, 1943. (147.) Pratt, G. K.: Ment. Hyg., 26, 39, 1942. (148.) Pratt, J. H.: War Med., 1, 358, 1941. (149.) Preston, G. H.: Ment. Hyg., 26, 33, 1942.

(150.) Rapaport, D.: Bull. Menn. Clin., 5, 146, 1941. (151.) Report of the Committee on National Defense of the Illinois Psychiatric Society, Dis. Nerv. Syst., 3, 127, 1942. (152.) Reynolds, C. L.: Mil. Surg., 90, 386, 1942. (153.) Rioch, D. McK., Jacobsen, C. F., Fingert, H. H., and Warson, S. R.: Psychiatry, 4, 331, 1941. (154.) Robie, T.: J. Med. Soc. New Jersey, 38, 398, 1941. (155.) Rosenberg, S. J., and Lambert, R. H.: Am. J. Psychiat., 99, 164, 1942.

(156.) Sargant, W., and Slater, E.: Lancet, 2, 1, 1940. (157.) Sargant, W., and Slater, N.: Lancet, 2, 212, 1941. (158.) Sargant, W., and Slater, E.: Proc. Roy. Soc. Med., 34, 757, 1941. (159.) Sargant, W.: Brit. Med. J., 2, 574, 1942. (160.) Saslow, M. S.: War Med., 1, 486, 1941. (161.) Saslow, M. S., and Junkerman, C. S.: War Med., 2, 99, 1942. (162.) Schuyler, D.: Dis. Nerv. Syst., 4, 89, 1943. (163.) Scoville, M. C.: Am. J. Psychiat., 99, 358, 1942. (164.) Selective Service Psychiatry, Psychiatry, 4, 440, 1941. (165.) Simon, A.: War Med., 1, 392, 1941. (166.) Simon, A., Hagan, M., and Hall, R. W.: War Med., 1, 387, 1941. (167.) Simon, A., and Hagan, M.: Am. J. Psychiat., 99, 348, 1942. (168.) Simon, A.: Illinois Psychiat. J., 2, 12, 1942. (169.) Skinner, E. F.: Clin. J., 71, 105, 1942. (170.) Slater, E.: Med. Press, 205, 133, 1941. (171.) Smith, L. H.: Psychiatry, 4, 241, 1941. (172.) Smith, L. H.: Med. Clin. North America, 25, 1717, 1941. (173.) Snowden, E. N.: Lancet, 2, 769, 1940. (174.) Solomon, A. P.: Dis. Nerv. Syst., 4, 78, 1943. (175.) Sommer, C. S., and Weinberg, J.: Dis. Nerv. Syst., 4, 70, 1943. (176.) Stearns, A. W.: Acute Psychoses and Acute Confusional States in the Military Service, Collected Lectures of the Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including Military Psychiatry, p. 83, Metropolitan State Hospital, Waltham, Mass., 1942. (177.) Stearns, A. W.: Examination of Recruits, Detection of the Commoner Psychotic and Neuropathic Traits, Collected Lectures of Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including Military Psychiatry, p. 19, Metropolitan State Hosp., Waltham, Mass., 1942. (178.) Steckel, H. A.: Ment. Hyg., 25, 13, 1941. (179.) Stein, C.: U. S. Nav. Med. Bull., 41, 142, 1943. (180.) Stilwell, L. E., and Schreiber, J.: War Med., 3, 20, 1943. (181.) Sullivan, H. S.: Psychiatry, 4, 201, 1941. (182.) Sullivan, H. S.: Psychiatry, 4, 203, 1941. (183.) Sullivan, H. S.: Ment. Hyg., 26, 7, 1942. (184.) Surgeon General, U. S. Army; Circular Letter No. 19: War Med., 1, 418, 1941. (185.) Sutherland, J. D.: Brit. Med J., 2, 365, 1941. (186.) Sutton, D. G.: Am. J. Psychiat., 97, 255, 1940. (187.) Sutton, D. G.: Psychiatry, 4, 219, 1941.

(188.) Tarumianz, M. A.: Delaware State Med. J., 14, 77, 1942. (189.) Thom, A.: New England J. Med., 225, 564, 1941. (190.) Thom, D. A.: J. Lab. and Clin. Med., 23,

499, 1943. (191.) **Tillisch, J. H.**, and **Walsh, M. N.**: War Med., 2, 917, 1942. (192.) **Tillman, C. G. D.**: Bull. Menn. Clin., 5, 167, 1941. (193.) **Tredgold, R. F.**: J. Ment. Sci., 88, 444, 1942. (194.) **Trippe, C. M.**: J. Med. Soc. New Jersey, 39, 524, 1942. (195.) **von Storch, T. J. C.**, **Pratt, G. O.**, **Farrell, M. J.**, **Currier, D. E.**, and **Viets, H. R.**: New England J. Med., 224, 890, 1941. (196.) **von Storch, T. J. C.**, and **Pratt, G. O.**: Mil. Surg., 88, 627, 1941.
(197.) **Wells, F. L.**: Examination of Recruits, Practical Psychometric Tests, Collected Lectures of the Seventh Post-Graduate Seminar in Neurology and Psychiatry, Including Military Psychiatry, p. 13, Metropolitan State Hospital, Waltham, Mass., 1942. (198.) **Williams, G. D.**: Army Med. Bull., No. 65, p. 105, 1943. (199.) **Williams, V. P.**: New England J. Med., 226, 302, 1942. (200.) **Wilson, A. T. M.**: The Practitioner, 146, 254, 1941. (201.) **Wilson, S. C.**: Occupat. Ther. and Rehabil., 20, 255, 1941. (202.) **Wittkower, E.**, and **Spillane, J. P.**: Brit. Med. J., 1, 223, 1940. (203.) **Wittson, C. L.**, **Harris, H. I.**, **Hunt, W. A.**, and **Solomon, P.**: War Med., 2, 944, 1942. (204.) **Wolfson**: Quoted by Gillespie, R. D., Psychological Effects of War on Citizen and Soldier, New York, Norton & Co., p. 168, 1942.
(205.) **Youngman, N. V.**: Med. J. Australia, 1, 283, 1942.
(206.) **Zabriskie, E. G.**, and **Brush, A. L.**: Psychosomat. Med., 3, 295, 1941.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF MAY 18, 1943

Physiological Treatment of Burns by Means of a New Analgesic Ointment. R. BEUTNER (Department of Pharmacology, Hahnemann Medical College). Local anesthesia of burns cannot be obtained with water-soluble local anesthetics since they are too readily absorbed from the wound surface; moreover some are quite toxic and many burn "medications" are actually caustic. If they exert an anesthetic action this comes through destruction of nerve fibers along with other tissue. To test which anesthetic would be suitable for burn treatment we tested several medicaments, routinely used on burns, on rabbit eye. Most of these are claimed to give anesthesia, but they are also irritant and destroy tissue including nerve fibers. Along with anesthesia, a good burn remedy should: (1) Counteract inflammation; (2) have a low systemic toxicity; (3) have some disinfecting, bacteriostatic action.

Tannic acid being astringent inhibits inflammation but is highly irritant, toxic internally and devoid of bacteriostasis. "Triple dyes," picric acid, and sulfa drugs were also found to be irritant when tested on rabbit eye, and there is evidence that they irritate wound surfaces. Picric acid is nephrotoxic.

Analgesic treatment for burns conforming to the above requirements was found in benzocaine (ethyl aminobenzoate) which, although water-insoluble, is an efficient topical anesthetic (Tainter). Dissolved in fat it loses its anesthetic power. But by emulsifying it in water using the method of R. Beutner and K. R. Beutner, we achieved a stable suspension of benzocaine in an emulsion of a synthetic resin. This resin inhibits cutaneous inflammation, cutaneous erythema and swelling promptly disappearing. Such an emulsion of benzocaine in 0.5% concentration anesthetizes the rabbit eye without irritation. Its internal toxicity is negligible and it produces bacteriostasis. After addition of suitable thickening this emulsion has the appearance of an ointment. It was used in the treatment of 50 cases of second and third degree burns. It anesthetizes burns so as to obviate the use of morphine; healing was very satisfactory.

The Influence of Intestinal Acidity on the Gastric Secretion. M. H. F. FRIEDMAN, I. J. PINCUS and J. EARL THOMAS (Department of Physiology, Jefferson Medical College). Previously this laboratory reported that intraduodenal instillation of acid inhibits gastric secretion in response to a meal only if a threshold level of duodenal pH (approximately 2.5) is attained (*Proc. Soc. Exp. Biol. and Med.*, 51, 367, 1942). This was confirmed in these experiments. In addition, we found that insulin-provoked secretion in the Pavlov pouch dog is likewise inhibited by an adequately acid duodenal content but that histamine-provoked secretion is not. Secretion from the Pavlov pouch due to introduction of food (beef heart) into the main stomach and also secretion from the Heidenhain pouch due to the feeding of the meal were depressed when acid was infused into the duodenum.

Duodenal instillation of acid to the fasting dog does not affect the volume of gastric secretion, but does increase the total output of pepsin. Intraduodenal introduction of acid following a meat meal also increases the output of pepsin from the Pavlov pouch, providing the duodenal pH is not depressed too much and the volume of secretion is not inhibited. No increase in pepsin was noted in similar experiments when secretion was provoked by histamine.

In all experiments following intraduodenal instillation of acid there was an after-effect of increased rate of gastric secretion providing a secretory stimulus (food, histamine) was still acting. This after-effect was not always related to the previous inhibition since it occurred even in those experiments where the acid did not result in gastric secretory inhibition.

These experiments suggest an emergency mechanism for the autoregulation of gastric secretion set into action when a dangerous threshold degree of acidity in the intestine is reached. The factors involved are still obscure. Acid in the intestine would seem to have a definite pepsigogue effect, providing the acidity is not too high. The after-effect of increased gastric secretion may be due to hydration following the intestinal introduction of large volumes of fluid.

The Metabolism of "Folic Acid." L. D. WRIGHT and A. D. WELCH (The Nutritional Laboratories, Medical Research Division, Sharp & Dohme, Inc., Glenolden, Pa.). "Folic acid," probably identical with vitamin Bc and the lactobacillus casei eluate factor, unlike other members of the vitamin B complex, is excreted only in traces in the urine of man. The urine contains, however, a substance which on incubation with surviving rat liver is converted into "folic acid." The yield of the substance in urine is increased by autoclaving for $1\frac{1}{2}$ hours in the presence of normal HCl. Since "folic acid" is destroyed by such treatment these findings suggest that a stable fragment of "folic acid" is excreted in the urine and that this is modified, probably through conjugation, by rat liver tissue to "folic acid"; the liver reaction is enzymatic. The urine factor has been concentrated by adsorption on and elution from superfiltrol to a potential activity approximately 2000 times that of urine. Its adsorption characteristics resemble those of "folic acid." Acid autoclaving of a grass juice concentrate and a liver concentrate, both good sources of "folic acid," destroyed the "folic acid" present. On incubation with liver the "folic acid" activity of the grass juice was restored. Under similar conditions a several-fold increase in the "folic acid" content of the liver occurred.

When synthetic xanthopterin is incubated with liver more "folic acid"

is usually found after microbiologic assay than can be accounted for on the basis of the "folic acid" content of the liver alone. Possibly uropterin, said to be identical with xanthopterin, is the substance in urine which is capable of enzymatic conversion to "folic acid." Such a hypothesis suggests that "folic acid" is a conjugate of which xanthopterin is one moiety.

Using these techniques, and others, the relationship of xanthopterin to "folic acid" and the nature of the residual portion of the molecule are being investigated further.

A Comparison Between Insulin and Phlorhizin in the Treatment of Early Pituitary-Diabetes. F. D. W. LUKENS and F. C. DOHAN (The George S. Cox Medical Research Institute, University of Pennsylvania). Partially depancreatized cats have been made diabetic by anterior pituitary extract as previously reported, and treated within the first 3 months of diabetes with insulin or with phlorhizin. Each drug was discontinued after 3 to 4 weeks of treatment, and sustained functional recovery of the animal was observed. In order to evaluate these two therapeutic agents, the similarities and contrasts between them have been reviewed on the basis of our results and of the literature. Both insulin and phlorhizin reduced the diabetic hyperglycemia to normal levels and brought about the morphologic restoration of the islands of Langerhans. They appeared to differ in the primary site of action, and in their effects on protein catabolism, ketogenesis, the storage and oxidation of carbohydrate and glycogen formation. Although our knowledge of these functions is incomplete, the results with phlorhizin provide a new type of evidence showing that hyperglycemia is one of the factors involved in the production of island damage and diabetes.

The Ability of Homocystine to Support Rat Growth in the Absence of Dietary Choline and Methionine. MARY A. BENNETT, GERRIT TOENNIES and GRACE MEDES (Lankenau Hospital Research Institute). In our laboratory young rats have repeatedly been found to grow on methionine and choline-free diets supplemented with homocystine. To investigate this phenomenon, female albino rats 5 weeks old were placed on an amino acid-corn oil diet* with 8 B vitamins being administered according to Bennett and Toennies.† After 4 days, daily supplements of 18, 36 and 54 mg. dl-homocystine (fed separately in butter)‡ were given to 6 animals each (Groups A, B, C), resulting in average daily weight gains of 0.6, 1.2 and 1.2 gm., on average daily basal food consumptions of 2.7, 4.0 and 3.8 gm., respectively. Growth occurred in the absence of butter, but not in the absence of homocystine.

In some animals growth has continued undiminished for more than 2 months, in others it has decreased, and in some an abrupt drop in weight at a rate of 3 gm. or more per day occurs, with basal food consumption declining to zero. One animal of Group A began this drop on the 39th day of homocystine feeding, one of Group B on the 21st day, and 3 of Group C

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* CHANDLER, J. P., and DU VIGNEAUD, V.: J. Biol. Chem., 135, 223, 1940; 2-methyl-1, 4-naphthoquinone (10 per gram of food) was added to the fat-soluble vitamins; homocystine was omitted from the mixture; analysis confirmed absence of methionine and choline.

† BENNETT, M. A., and TOENNIES, G.: J. Biol. Chem., 145, 671, 1942.

‡ BENNETT, M. A.: Biochem. J., 33, 1794, 1939; butter, as well as corn oil, were washed with acid and water.

on the 21st, 39th and 62d day, respectively. Upon addition of choline to the homocystine supplements, eating and growth were resumed after 6 to 9 days of decline; withdrawal of choline after attainment of the former maximum weight resulted in continued growth for one to as much as 4 weeks, climaxed by another drop similar to the former. To date 3 cases have been observed where the new decline ended with spontaneous (without choline) resumption of eating and growth.

Preliminary results indicate that the growth rates of animals receiving homocystine are greatly reduced when our supplement of B vitamins is replaced by the ryzamin-B, thiamin, riboflavin, nicotinic acid combination of du Vigneaud and Chandler.*

* See Footnote, * page 129.

BOOK · REVIEWS AND NOTICES

ARCHIVES OF BIOCHEMISTRY, Vol. I, No. 3, 1943. New York: Academic
 Press, Inc. Price, 2 vols. a year at $5.50 each.

THE advent of a second journal in the United States devoted to biochemistry
should be hailed with approval and anticipation by those interested in the
development of the subject. England, Japan, Russia, and the United States
have long had one biochemical journal. Germany, for many years, has had
two. The very large research activity in biochemistry now, to say nothing
of its anticipated increase during and after the war, will undoubtedly make
available much material to keep the pages of the new journal full.

The Editorial Board is composed of well-known men in the biochemical
field in this country: M. L. Crossley, American Cyanamid Company, Bound
Brook, N. J.; F. C. Koch, Armour & Co., Chicago, Ill.; E. O. Kraemer, The
Biochemical Research Foundation, Newark, Del.; C. M. McCay, Cornell
University, Ithaca, N. Y.; F. F. Nord, Fordham University, New York, N. Y.;
F. W. Went, California Institute of Technology, Pasadena, Calif.; C. H.
Werkman, Iowa State College, Ames, Iowa.

The development and character of this new journal will be watched with
interest by biochemists. W. S.

INTRODUCTION TO ORGANIC AND BIOLOGICAL CHEMISTRY. By L. EARLE
 ARNOW, PH.D., M.D., Director of Biochemical Research, Medical Research
 Division, Sharp & Dohme, Inc., Glenolden, Pa.; Formerly Assistant Professor
 of Physiological Chemistry, University of Minnesota Medical School; and
 HENRY C. REITZ, PH.D., Assistant Chemist in the Western Regional
 Research Lab., U. S. Dept. of Agriculture, Albany, Calif.; Formerly Assistant
 Professor of Agricultural Biochemistry, University of Minnesota. Pp. 736;
 90 figs., many tables. St. Louis: C. V. Mosby Company, 1943. Price,
 $4.25.

THIS volume is designed particularly for students in pre-medical, pre-dental,
home economics and similar fields of study. A short review of chemical
fundamentals, 53 pages, is followed by 480 pages devoted to organic chemistry,
and 160 pages to biologic chemistry. The usual classes of organic compounds
are considered, emphasis being placed upon interrelationships of the various
types of compounds. In the section on biologic chemistry the digestion, inter-
mediary metabolism and excretory products of each of the major groups of
organic compounds are treated as a unit. Chapters on hormones, vitamins,
enzymes and a summary of nutritional requirements complete the book. A
series of study questions accompanies each chapter. H. V.

THE PREMATURE INFANT, ITS MEDICAL AND NURSING CARE. By JULIUS H.
 HESS, M.D., Professor of Pediatrics, University of Illinois College of Medi-
 cine, Chicago, and EVELYN C. LUNDEEN, R.N., Supervisor, Premature
 Infant Station, Sarah Morris Hospital, Chicago. Pp. 350; 77 illus. Phila-
 delphia: J. B. Lippincott Company, 1941. Price, $3.50.

THIS is an excellent presentation of the care of the premature baby, embody-
ing the joint experience of the pediatrician-in-chief and the nursing supervisor
of one of the best known and best run premature infant stations in this country.
Emphasizing practice rather than theory, it is comprehensive, authoritative,

and well organized and illustrated.   The book can be highly recommended as a handbook and guide for use by interns, nurses, and all members of a hospital team which assume the multitudinous special responsibilities of this important and difficult branch of pediatrics.   I. W.

PROBLEMS OF AGING, THE BIOLOGICAL AND MEDICAL ASPECTS.   Edited by EDMUND VINCENT COWDRY, PH.D.   A publication of the Josiah Macy Junior Foundation.   Second Edition.   Pp. 972; 129 illus.   Baltimore: The Williams & Wilkins Company, 1942.   Price, $10.00.

ALL who have given the subject serious consideration will agree that today old age has assumed importance as a problem of far-reaching medical, social, economic and even political significance.   This is the result of two definite and related factors that have been exerting a marked influence on our national life for many years, namely, the noteworthy increase in life expectancy that has occurred since the beginning of this century and the changing trend in the age composition of our population.   It is not surprising, therefore, that the past decade has been marked by the awakening of a lively interest in the various aspects of Gerontology.   The present volume furnishes impressive evidence that the problems of aging have attracted the attention of many of our ablest thinkers in the various fields of the biologic and medical sciences.

The first edition of this book, published in 1939, was enthusiastically received as the first attempt to deal with the problems of growing old along broad biologic lines.   This new edition should attain even greater popularity, embodying as it does the excellence of the earlier work with much additional material of value and interest.

Nine new chapters representing the work of 11 additional authors have been added in the second edition, making the volume over 250 pages longer than the original edition.   The material in the first edition has been carefully revised and in many instances greatly elaborated.   The work represents a series of essays by specialists of outstanding experience well qualified to deal with the varied aspects of the age problem.   It is the only book that makes available to the student of Gerontology the fundamental biologic data along with the broad psychologic, sociologic, as well as the more practical medical aspects of the process of aging.   The author, the editor, is to be congratulated upon the admirable way in which the vast fund of knowledge contained in this volume has been integrated.   This book is indispensible to all, scientists and laymen alike, who are concerned with the problems of aging.   Furthermore, it fulfils a timely and useful purpose, inasmuch as it emphasizes the challenge of old age to present-day civilization and the obligation which now rests upon Society to successfully meet that challenge.   G. P.

contributors have well accomplished this task set before them. The earlier chapters are devoted to the metabolism of fats, proteins, carbohydrates, minerals, and water. About 150 pages are devoted to the vitamins, followed by chapters on undernutrition, obesity, xanthomatoses, glycogen disease, and gout. Hyperinsulinism, diabetes insipidus, and mellituria precede a 200 page treatise on diabetes mellitus. In the appendix is an extensive list of foods and their composition in addition to several other tables used more commonly in metabolic studies.   M. T.

TEXT–BOOK OF PATHOLOGY. By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL., PSYCH., F.R.S.C., Professor of Pathology and Bacteriology in the University of Toronto; Formerly Professor of Pathology in the University of Manitoba, Winnipeg, Canada. Fourth Edition. Pp. 1008; 490 engravings (29 colored plates). Philadelphia: Lea & Febiger, 1943. Price, $10.00.

THE aura surrounding literary first editions should not conceal the fact that scientific text-books are apt to improve with each succeeding edition, and "Boyd" is no exception. It is rare, however, where the corpus of knowledge of a given subject is steadily increasing, to find an author who succeeds in such deletions and condensations, "through a tightening of the belt of speech," that the new edition is 56 pages shorter than its predecessor. "Among the principal deletions are the chapter on 'The Body Constants in Disease,' and the sections on immunity and hypersensitiveness, which are subjects that are dealt with more adequately in books on immunology, the section on the principles of heredity, as well as much bacteriologic detail in the chapter on 'Bacterial Infections.' The following new additions, some quite brief, may be mentioned: vitamin K and heparin in relation to thrombosis, histoplasmosis, actinobacillosis, liposarcoma, liver necrosis in burns, spread of tumors by the vertebral system of veins, subacute myocarditis of unknown etiology, disseminated lupus erythematosus, virus pneumonia and radiation pneumonitis, cystic fibrosis of the pancreas, lycopodium peritonitis, the renal juxtaglomerular apparatus, the relation of the kidney to hypertension, intercapillary glomerulofibrosis, crush nephritis, non-glomerular and extrarenal uremia, Hunner's ulcer, the relation of blood phosphatase to carcinoma of the prostate, interstitial endometrioma, fibrosing adenomatosis of the breast, Hürthle-cell tumor, Boeck's sarcoid, the Rh factor in erythroblastosis fetalis, Marchiafava-Micheli paroxysmal hemoglobinuria, equine encephalomyelitis, Wernicke's disease, and lesions of the intervertebral disks. Sections which have been largely or in part rewritten include those on the etiology of tumors, cirrhosis of the liver, goiter, acute intestinal obstruction, the pathologic physiology of the spleen, nephrosis, etiologic agents in breast carcinoma, arteriolar sclerosis, the etiology of atheroma, of cholecystitis and of diabetes, pyelonephritis, the pathogenesis of lobar pneumonia, constrictive pericarditis, endometriosis, the etiology of poliomyelitis, and laceration of the brain."

The good features of this text-book, which make it so popular with our medical students, have been pointed out in this Journal in the reviews of earlier numbers. Its shortcomings grow steadily less with each edition. This is but one more reason for hoping that there will be many more editions.   E. K.

MIND, MEDICINE, and MAN. By GREGORY ZILBOORG, M.D. With a Foreword by ARTHUR H. RUGGLES, M.D. Pp. 344. New York: Harcourt, Brace & Co., Inc., 1943. Price, $3.50.

IN language appropriate to laymen, this psychiatrist tells how his specialty is today concerned with maladjustment, with science, crime, war and religion. The chapters given most space are: Certain Misconceptions, Crime and Judgment, and that of Psyche, Soul and Religion; other chapters are instincts

and Their Manifestations, Normal Neuroses and Personality, Certain Aspects of Mental Illness, Theories and Practice, Civilization and Social Sciences, and Varieties of Human Aggression. The able discussion on medical jurisprudence began with that of Babylon 4000 years ago. High tribute is paid to Freud whose psychoanalysis permeates the entire work. The Master's want of sympathy for all forms of religion is discussed; the defense offered in his behalf is not very satisfying. Freud's "depth psychology" is not so deep as that to be found in the venerable Yoga system—of which William James wrote enthusiastically—the advance phase of which occupies an exalted religious plane. For one of foreign birth and education, the author writes with great clarity and furnishes interesting reading.   N. Y.

OPERATING ROOM TECHNIQUE. By EDYTHE LOUISE ALEXANDER, R.N., Supervisor of the Operating Rooms of The Roosevelt Hospital, New York City. Pp. 392; 221 illus. St. Louis: C. V. Mosby Company, 1943. Price, $3.75.

THIS monograph should be of interest to the teaching staff of a nurses training school, particularly to those concerned with surgical procedures. It is probable that assistant surgeons, surgical residents and fellows and surgical interns would benefit from its detailed descriptions. Throughout the text, teamwork is stressed as essential to the safeguarding of the surgical patient.

The early part of the book reviews the ideal arrangement of an operating room with emphasis on its care and cleaning. The chapter on Sterilization is concise and well outlined. In the discussion of suture material, an historical background is given together with a thorough description of various kinds. The inclusion of cotton suture material would complete the presentation.

Two-thirds of the book is devoted to reviewing operative cases in detail. The gastro-intestinal chapter is cleverly introduced with a treatise on aseptic technique.

The illustrations are excellent. In criticism one questions the omission of a bibliography.   L. S.

MEDICAL RELIEF IN EUROPE. Questions for Immediate Study. By MELVILLE D. MACKENZIE, M.D. Pp. 67. London: Royal Inst. of International Affairs, 1942. Price, 2s. net.

THIS small book represents a scholarly attempt "to depict the post-war medical picture as far as this can be foreseen, and to outline a number of practical considerations whose importance from a medical point of view has been emphasized from past experience." It was prepared for the learned Royal Institute of International Affairs as one of a series of monographs devoted to an unofficial and unpolitical inquiry into Britain's policies and responsibilities toward Europe after the current war. The chapters deal with such matters as the sociologic factors contributing the post-war medical problems, the modus operandi for post-war medical relief, the handling of specific public health problems such as starvation, malaria and typhus, and the necessity for re-establishing a permanent international health organization to replace the defunct International Health Office in Paris and the Health Organization of the League of Nations. In addition to sketching in the skeletal contours of a rounded all-Europe relief program, the author discusses many problems in fascinating detail, citing experiences from the last Great War in order to establish the validity of recommendations for the conduct of relief in this even greater war. Thus, to select an example at random, the medico-legal aspects of cannibalism during famine are considered. In at least one area of Europe during 1919 to 1921 human beings, usually children, were killed and eaten by gangs of starving people. Even when other food was made available the practice continued at times, owing either to an acquired taste for this kind of meat or because the murderers were political outlaws from their communities

and unable to come in for supplies. When presented with such a situation the medical relief officer will have to decide by examination whether an offender when caught was mentally irresponsible at the time because of famine or illness, or whether the killing had been clear-mindedly and deliberately done. The decision must be made upon the individual's mental attitude. If he discusses the act unhesitatingly and without shame, or even refers to the satisfaction derived from killing, he should be judged, generally speaking, as a psychiatric patient morally irresponsible for his action. On the other hand, if he attempts to hide or deny what has been done or refuses to discuss the killing, the assumption is suggested that he has been knowingly aware of committing murder and should therefore be considered as a criminal liable to the death penalty. Certainly a type of problem requiring judgment and advance training on the part of the authority-holding medical officer!

At the close of the last war a full program for relief was not ready. There was tragic delay in getting aid to the conquered countries and chaotic confusion and costly overlapping occurred among the various international and national relief organizations which were hurriedly set up. In fact, during the 3 years following the armistice more souls died from starvation and preventable disease than were killed in the war itself. To avoid repetition of such a terrible tragedy in the years to come it is imperative to make careful preparations now, before the present war is over, for a well-organized and central administrative machine containing representatives from all the allied governments. Such an organization or committee "would serve to coördinate the various departmental activities of the governments supplying relief, especially those concerned with such vital questions as priorities, transport, food supplies, medical problems, economic reconstruction, agriculture, fishing, etc." On the shoulders of a Medical Sub-committee should rest the problems of restoring the nutrition of the hungry and the treatment and prevention of epidemic disease. To the work and organization of the medical sub-committee the subject-matter of this book is devoted.   I. W.

BRONCHIECTASIS. By JAMES R. LISA, Pathologist, City Hospital, Welfare Island, and MILTON B. ROSENBLATT, Associate Visiting Physician, City Hospital, Welfare Island. Pp. 190; 45 illus. New York: Oxford University Press, 1943. Price, $4.00.

THE authors of this small monograph are to be congratulated for the excellent manner in which they have presented the subject. They have considered the anatomy and physiology of the bronchi, the theories of the etiology, pathogenesis and pathology of the process. There is an extensive bibliography. As most of the literature was controversial, they have studied their own material critically in the light of the reports in the literature and have discussed briefly the clinical and Roentgen manifestations of the condition and its treatment.

One is impressed with the excellence of the pathologic discussion, and of the large number of illustrations, showing the various types of pathologic changes in bronchiectasis.

The Reviewer, in this instance a radiologist, was disappointed in there being so little effort to correlate the Roentgen and pathologic manifestations. Lack of attention to this detail is an important omission because the radiologic aspects of bronchiectasis are much relied upon by all clinicians. The authors have, however, called attention to the fact that the negative Roentgen ray examination cannot be regarded necessarily as evidence against bronchiectasis being present. The authors, however, have not discussed the manner in which bronchography is done, especially in those instances where lobectomy is being considered. Likewise, they have failed to discuss how bronchiectasis affects the dynamics of the bronchial tree and its contiguous structures, both important items in determining whether the condition is reversible or not. Another omission has had to do with the drainage of the lipiodol from the lung paren-

chyma and bronchi in normal and abnormal lung structures. They have not discussed the differences in appearances in those cases in whom bronchography is performed without having had the lungs aspirated and those that have had aspiration performed and then bronchography performed. These radiologic considerations are important in evaluating the extent and the character of the bronchiectasis. Despite this omission the monograph is an excellent contribution and is recommended to anyone interested in this subject.

The publishers are to be praised for the excellence of the paper, illustrations, print and general set-up of the monograph.   E. P.

VASCULAR SCLEROSIS WITH SPECIAL REFERENCE TO ARTERIOSCLEROSIS: Pathology, Pathogenesis, Etiology, Diagnosis, Prognosis, Treatment. By ELI MOSCHCOWITZ, A.B., M.D., Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York; Physician, Mt. Sinai Hospital, New York; Consulting Physician, Beth El Hospital, Brooklyn, N. Y.; Consulting Pathologist, Beth Israel Hospital, New York. Pp. 178; 43 illus. New York, Toronto, and London: Oxford University Press, 1942. Price, $3.75.

THIS relatively small monograph represents a summary and amplification of the author's work on this subject during the past 25 years. It favors three principles, which are well presented: "first, the biology of the diseased processes; second, the mechanistic genesis of arteriosclerosis; and third, the psychosomatic interpretation of certain forms of essential hypertension." Pulmonary, capillary, venous, and endocardial sclerosis are included in the subject matter. A concise but adequate chapter on treatment is also included. The most striking feature of this volume is the collection and integration of data along with the author's personal observations. His evaluation and interpretation of this material is in line with the mechanistic theory of the origin of arteriosclerosis. He does not, however, deny the presence of other conditioning factors. This book is easy to read and gives stimulating food for thought to both the clinician and pathologist.   M. T.

SYNOPSIS OF DISEASES OF THE SKIN. By RICHARD L. SUTTON, M.D., Emeritus Professor of Dermatology, University of Kansas Medical School; and RICHARD L. SUTTON, JR., M.D., Assistant Professor of Dermatology, University of Kansas Medical School. Pp. 481; 413 illus. St. Louis: C. V. Mosby Company, 1942. Price, $5.50.

A REMARKABLE amount of information is included in this relatively small book. The materials are down to date and richly illustrated by excellent photographs, which average one to the page. This is most important in a subject like dermatology. For the students the book is adequate, and for the clinician it should suffice for ordinary working purposes.

The book is of such a size that it can be easily slipped into the pocket, is attractively and sturdily bound, and printed on enamel paper. The Reviewer feels that it is the best of the shorter treatises on dermatology.   F. W.

author's characteristic wit. The quantitative measurement of materials so commonly found in scientific reports of this nature and discussion of the inheritance of complicated traits are not presented, as this was not within the scope or purpose of the author. Nevertheless, the book does embody a large collection of scientific material which can be useful to the scientist, and in addition the author presents many unsolved problems. This book justifies a wide and useful circulation.   M. T.

ATLAS OF OVARIAN TUMORS. By GEMMA BARZILAI, M.D. Preface by FRED W. STEWART, M.D., Pathologist, Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York City. Pp. 264, 258 illus. (45 in color). New York: Grune & Stratton, 1943. Price, $10.00.

THIS is essentially an atlas of microscopic diagnosis, illustrated by excellent photomicrographs and colored drawings and designed to present both coarse and fine microscopic detail as may be found in the different appearances of ovarian tumors. This timely presentation has been well done, and is reasonably complete. Some of the rarer and not characteristically ovarian tumors are omitted. The morphology, histogenesis, and other features of each neoplasm are systematically described in the text, which is concise and adequate in most instances. The author labels the more commonly called serous cystadenomas as "endosalpingiomas," in accordance with his belief of the histogenesis of this tumor. Likewise, he prefers the term "seroanaplastic carcinoma" to adenocarcinoma. The chapter on secondary ovarian tumors is largely devoted to Krukenberg tumors. The book has a plastic binding, which lends to its easy use. A few typographical and grammatical errors are present. As a whole, the author has succeeded well in compiling and presenting this atlas in a well-organized and very useful manner.   M. T.

A HANDBOOK ON DISEASES OF CHILDREN, INCLUDING DIETETICS AND THE COMMON FEVERS. By BRUCE WILLIAMSON, M.D., F.R.C.P., London, England. Pp. 364; 70 illus. Baltimore: The Williams & Wilkins Company, 1942. Price, $4.50.

THE general practitioner who feels the need of a synopsis of pediatrics to be carried about as a jog to memory may be interested in this small handbook. The main clinical manifestations of the common ailments of childhood are described briefly, and suggestions given as to treatment. The section on artificial feeding reflects the English rather than the modern American point of view; most of the proprietary foods recommended are not known in this country. One notes that evaporated milk receives nearly no mention, and that "the feeding-bottle should be of the boat-shaped variety and should be open at each end and devoid of corners." The book suffers also by not describing laboratory tests and roentgenograms as aids to diagnosis in early and difficult cases. Several pages of useful prescriptions are given at the end.   I. W.

THE MEDICAL CLINICS OF NORTH AMERICA (Vol. 27, No. 2), March, 1943. Pp. 600; many illus. Philadelphia: W. B. Saunders Company, 1943. Price, year, $16.00. ·

THIS volume treats in detail most of the important aspects of nutrition. The various sections are treated in scholarly fashion by individuals thoroughly familiar with the field. There is, as is inevitable in a volume of this kind, some duplication and there are also some conflicting points of view. An effort is made to stroke a balance between points of view with respect to nutrition; in certain instances this results merely in superficiality in both departments. However, with careful reading, anyone interested in the subject of nutrition, be he scientist or clinician, may find much to instruct him in this book.
                                                               K. E.

NEW BOOKS

Transureteral Prostatectomy. By REED M. NESBIT, M.D., F.A.C.S., Associate Professor of Surgery, University of Michigan Medical School, in charge of the Section of Urology, Department of Surgery. With original drawings illustrating techniques by WILLIAM P. DIDUSCH. A chapter on the Vascular Supply of the Prostate Gland by RUBIN H. FLOCKS, M.D. Pp. 201; 62 plates. Springfield, Ill.: Charles C Thomas, 1943. Price, $7.50.

The Neuromuscular Maturation of the Human Infant. By MYRTLE B. McGRAW, Associate Director, The Normal Child Development Study, Department of Pediatrics, Columbia-Presbyterian Medical Center. Pp. 154; illus. Morningside Heights, N. Y.: Columbia University Press, 1943. Price, $10.00.

The Chemistry of Natural Coloring Matters. By FRITZ MAYER, PH.D., Formerly Professor of Chemistry in the University of Frankfort-on-Main. Translated and revised by A. H. COOK, PH.D., Department of Chemistry, Imperial College of Science, London. American Chemical Society Monograph Series. Pp. 354; many figs. New York: Reinhold Publishing Corp., 1943. Price, $10.00.

Ways of the Weather. By W. J. HUMPHREYS, A.B., C.E. PH.D., Sc.D., Meterological Physicist (Retired, Collaborator), U. S. Weather Bureau. Pp. 400; 75 figs. Lancaster, Pa.: The Jaques Cattell Press, 1942. Price, $4.00.

Clinical Significance of the Blood in Tuberculosis. By GULLI LINDH MULLER, M.D., Pathologist and Director of Laboratory, New England Hospital for Women and Children, Boston; Formerly Pathologist, Rutland State Sanatorium, Rutland, Mass. Pp. 536; charts and tables. New York: The Commonwealth Fund, 1943. Price, $3.50.

Gynecology. By LAWRENCE R. WHARTON, PH.B., M.D., Associate in Gynecology, The Johns Hopkins Medical School; Assistant Attending Gynecologist, The Johns Hopkins Hospital; Consultant in Gynecology, The Union Memorial Hospital, Hospital for Women of Maryland, Sinai Hospital and Church Home and Infirmary. Pp. 1006; 444 illus. Philadelphia and London, W. B. Saunders Company, 1943. Price, $10.00.

An Introduction to Group Therapy. By S. R. SLAVSON, Director of Group Therapy, Jewish Board of Guardians, New York; Formerly Lecturer, School of Education, New York University. Pp. 352. New York: The Commonwealth Fund, 1943. Price, $2.00.

A Manual of Pulmonary Tuberculosis and An Atlas of Thoracic Roentgenology. By DAVID O. N. LINDBERG, M.D., F.A.C.P., Lecturer on Tuberculosis, State University of Iowa, College of Medicine; Director of Roentgenology, State Sanatorium, Iowa. Pp. 233; 145 figs. Springfield, Ill.: Charles C Thomas, 1943. Price, $6.50.

Behavior and Neurosis. By JULES H. MASSERMAN, M.D., Assistant Professor of Psychiatry, University of Chicago and Research Associate, Otho S. A. Sprague Memorial Institute, Chicago. Pp. 269; 7 plates. Chicago: The University of Chicago Press, 1943. Price, $3.00.

Physiology in Aviation. By CHALMER L. GEMMILL, B.S., M.D., Commander, M. C., U. S. N. R., Associate Professor in Physiology, The Johns Hopkins University, School of Medicine, Baltimore, Md.; Instructor in Physiology, School of Medicine, Naval Air Station, Pensacola, Fla. With a chapter on Instrument Flight by LT. FREDERICK B. LEE, U. S. N. R. Pp. 132; 18 figs. 18 tables. Springfield, Ill.: Charles C Thomas, 1943. Price, $2.00.

Allergy, Anaphylaxis and Immunotherapy. By BRET RATNER, M.D., Clinical Professor of Pediatrics, New York University College of Medicine; Visiting Pediatrician and Director of Pediatrics, Sea View Hospital; Associate Attending, Children's Medical Service, Bellevue Hospital; Consultant Pediatrician, French Hospital. Pp. 834; 88 figs. 26 tables. Baltimore, Md.: Williams & Wilkins Company, 1943. Price, $8.50.

Endometriosis. By JAMES R. GOODALL, O.B.E., B.A., M.D., C.M., D.Sc., F.I.C.S. (HON.), F.R.C.O.G., Formerly Professor of Clinical Gynecology and Obstetrics, McGill University; Consulting Staff in Gynecology and Obstetrics, Royal Victoria Montreal Maternity Hospital; Consulting Gynecologist and Obstetrician to the Homeopathic Hospital, Montreal; Consultant in Charge of Gynecology in St. Mary's Hospital, Montreal; Life-Fellow of the American Gynecological Society, etc. Pp. 140; 13 illus. in black and white; 16 color plates. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $5.50.

Essentials of Industrial Health. By C. O. SAPPINGTON, M.D., DR.P.H., Consulting Industrial Hygienist, President, Central States Society of Industrial Medicine and Surgery; Editor of "Industrial Medicine." Pp. 626; 63 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $6.50.

Medico-Legal Blood Group Determination. By DAVID HARLEY, M.D., B.Sc., F.I.C., The Laboratories of the Inoculation Department, St. Mary's Hospital, London. Pp. 119; 13 figs. London: Wm. Heinemann, Medical Books, Ltd., 1943. Grune & Stratton, Inc., New York, distributors in U. S. A. Price, 12s, 6d.

Somatic and Endocrine Studies of Puberal and Adolescent Boys. By WILLIAM W. GREULICH, PH.D., Departments of Anatomy and Anthropology, R. I. DORFMAN, PH.D., Department of Physiological Chemistry, H. R. CATCHPOLE, PH.D., Department of Physiology, C. I. SOLOMON, M.D., Department of Psychiatry and Mental Hygiene, C. S. CULOTTA, M.D., Department of Pediatrics, Adolescence Study Unit, School of Medicine and Institute of Human Relations, Yale University. Monographs of the Society for Research in Child Development, Vol. VII, No. 3 (serial No. 33). Pp. 85; 10 plates. Washington, D. C.: Society for Research in Child Development, National Research Council, 1942. Price, $1.50.

"This volume is a report of a study of some somatic and endocrine changes associated with puberty and adolescence." (Preface.)

Urology in General Practice. By NEISE F. OCKERBLAD, B.S., M.D., F.A.C.S., Professor of Clinical Urology, University of Kansas School of Medicine; Senior Attending Urologist to St. Luke's Hospital; Consulting Urologist to the Children's Mercy Hospital, Kansas City, Mo., and HJALMAR E. CARLSON, B.S., A.M., M.D., F.A.C.S., Instructor in Urology, University of Kansas School of Medicine; Attending Urologist to St. Luke's Hospital and Trinity Hospital, Kansas City, Mo. Pp. 383; 98 figs. Chicago: The Year Book Publishers, 1943. Price, $4.00.

Vitamins and Hormones. Edited by ROBERT S. HARRIS, Associate Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, and KENNETH V. THIMANN, Associate Professor of Plant Physiology, Harvard University. Vol. I. Foreword by E. V. McCOLLUM, Johns Hopkins University. Pp. 452; many tables and figs. New York: Academic Press, Inc., 1943. Price, $6.50.

Medical Genetics. By LAURENCE H. SNYDER, Sc.D., Professor of Medical Genetics, The Ohio State University. Pp. 130; 24 figs. Durham, N. C.: Duke University Press, 1941. Price, $1.50.

As the Twig is Bent. By LESLIE H. HOHMAN, M.D., Associate in Psychiatry, Johns Hopkins Medical School; Assistant Visiting Psychiatrist to The Johns Hopkins Hospital. Pp. 291. New York: The Macmillan Company, 1943. Price, $2.50.

Medical Clinics of North America. Symposium on Infectious and Tropical Diseases. Vol. 27, No. 3. Pp. 280. Philadelphia and London: W. B. Saunders Company, 1943. Price, $12.00 year paperbound, $16.00 clothbound.

NEW EDITIONS

Clinical Roentgenology of the Cardiovascular System. By HUGO ROESLER, M.D., F.A.C.P., Associate Professor of Roentgenology and Cardiologist, Department of Medicine, Temple University School of Medicine; Cardiologist, Temple University Hospital, Philadelphia. Pp. 497; 337 figs. Springfield, Ill.: Charles C Thomas, 1943. Price, $7.50.

A Manual of Otology, Rhinology and Laryngology. By HOWARD CHARLES BALLENGER, M.D., F.A.C.S., Associate Professor of Otolaryngology, Northwestern University School of Medicine, Chicago. Second Edition. Pp. 331; 114 illus. (3 color plates). Philadelphia: Lea & Febiger, 1943. Price, $4.00.

The Physiological Basis of Medical Practice. By C. H. BEST, M.A., M.D., D.Sc. (LOND.), F.R.S., F.R.C.P. (CANADA), Professor and Head of Department of Physiology, Associate Director of the Connaught Laboratories, Research Associate in the Banting-Best Department of Medical Research, University of Toronto; and N. B. TAYLOR, M.D., F.R.S. (CANADA), F.R.C.S. (EDIN.), F.R.C.P. (CANADA), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Professor of Physiology, University of Toronto. Third Edition. Pp. 1942; 497 figs. Baltimore, Md.: Williams & Wilkins Company, 1943. Price, $10.00.

The usefulness of this book is proved by the numerous reprintings of its first two editions. This third edition has expanded to a volume of 1942 pages, and incorporates advances made in physiology within the last 3½ years, with revisions and rewriting of the matter contained in former editions. The book will be welcomed by all who appreciate having readily available well-selected physiologic data as a basis for sound understanding of disease.   I. Z.

Notice to Contributors. Manuscripts intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

Instructions to Contributors. MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

ORIGINAL ARTICLES

STUDIES ON THE TRANSMISSIBILITY OF MALARIA BY PLASMA TRANSFUSIONS*

By Eugene L. Lozner

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AND

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It has been demonstrated repeatedly[5,6,7,15] that human malaria may be transmitted by transfusions of the whole blood of individuals who have not suffered from clinical malaria for many years. The actual plasmodia have been demonstrated microscopically in the blood of such donors.[6,7,15] It has also been observed that the plasmodia causing human malaria will remain infective in whole blood preserved in the liquid state up to 8 days[1,2] and that animal malaria may be transmitted by whole blood frozen quickly at very low temperatures.[4,8] In view of the rapidly increasing use of transfusions of plasma preserved in the liquid, frozen and dried states, and of the large number of volunteer blood donors, some of whom may have had unrecognized malaria, participating in the plasma program for the Army and Navy, it became of considerable importance to determine the likelihood of transmission of malaria by means of plasma transfusions. Studies therefore were undertaken with this object in view, and it is the purpose of this communication to report the results of 35 administrations of plasma prepared from donors with active malaria, and preserved by different techniques for varying lengths of time.

Methods. The patients who served as donors for the blood to be processed into plasma and as the recipients of the plasma were on the wards of the St. Elizabeth's Hospital, Washington, D. C.† The donors were patients with active therapeutic quartan and estivo-autumnal malaria. The 35 recipients

were patients with general paresis or other central nervous system disease in which malaria was either indicated or not contraindicated.

Two hundred and fifty ml. of blood were drawn from each donor on the dates indicated in Table 1, into 35 ml. of 2.5% sodium citrate using a "closed-vacuum" system. "Thick" smears were made on the capillary blood of each donor at this time. On the same day on which the blood was drawn it was centrifuged at 2500 r.p.m. for 1 hour and then stored overnight at 8° C. On the following morning, the plasma was aspirated without filtration by means of a "closed-vacuum" system with scrupulously aseptic technique. No bacteriostatic was added and when the conditions of the protocol permitted it, bacteriologic cultures were done. Occasionally the plasma from 2 or 3 donors was pooled; usually it was not.

In view of the fact that most of the plasma being used by the armed services at present is dried from the frozen state, it was decided to study first the effects of freezing, since if it were found that freezing reduced the likelihood of transmission, the additional step of drying would prove unnecessary. Accordingly, in 20 instances, the plasma was "shell" frozen immediately after aspiration by horizontal rotation of the bottle in a bath of solid carbon dioxide and alcohol and then stored in the frozen state at −20° C. in a mechanical refrigerator. In 3 of the observations the plasma was dried from the frozen state by placing it in series with a condenser cooled by solid carbon dioxide and a high vacuum pump. When, as will be seen in Table 1, no transmissions were observed following the administration of frozen or dried plasma, the question arose as to whether plasma ever contained enough red cells to transmit malaria. To answer this, 12 administrations of plasma preserved in the liquid state from 1 day to 2 weeks were observed; this preservation was at room temperature averaging 20° to 25° C. When frozen plasma was to be administered, it was thawed in a water-bath at 37° C. on the morning of administration. When dried plasma was to be administered it was restored to the liquid state with an equivalent amount of sterile pyrogen-free distilled water immediately before administration. Administration of all plasma was by a standard intravenous set in which was incorporated a glass tape filter of pore size equivalent to a 150-mesh stainless steel filter for removal of fibrin shreds.

Control "thick" smears were made and examined on each recipient before injection. Despite this precaution, 2 of the recipients (Nos. 25 and 26) were discovered subsequently to have suffered malaria 5 and 10 years previously respectively. All injections were made intravenously. All recipients were followed by taking rectal temperatures twice daily and examining "thick" smears of capillary blood 3 times weekly for at least 9 weeks. This period was selected on the basis of Boyd's observations on 38 cases of quartan malaria artificially induced by whole blood, in whom the mean incubation period before detection of parasites was 9.5 days and in whom 37 of the 38 showed parasites in less than 30 days. All blood smears were stained with diluted Giemsa's stain and examined microscopically under oil by 2 observers.

Results. Thirty-five administrations of plasma prepared from patients with active malaria were made in dosages varying from 60 to 270 ml. No immediate untoward reaction was observed in any instance. A summary of the data concerning the administrations and the result of each is presented in Table 1.

It will be observed that in the 20 administrations of frozen and the 3 of dried plasma, no transmissions of malaria were observed. On the other hand, in the 2 administrations of plasma preserved in the liquid state for 1 day before injection, there was 1 definite transmission and 1 probable transmission, questionable only because the patient had had malaria 5 years previously. In the 5 administrations of plasma preserved in the liquid state for 1 week before injection, no transmissions

were observed except for 1 doubtful case who showed parasites on only one occasion, had no symptoms and turned out to have had malaria 10 years previously. In the 5 administrations of plasma preserved in the liquid state for 2 weeks, no transmissions were observed.

Discussion. It appears from the above findings that the danger of transmission of malaria by any plasma program, regardless of the type of preservation used, is minimal. The only definite transmission observed was caused by liquid plasma 1 day old. Since administration of plasma under 10 days old is performed rarely for reasons of bacteriologic control, it is evident that liquid plasma over 1 week old, frozen and dried plasma are all equally safe as regards malaria transmissibility.

The transmission of human malaria by whole blood preserved up to 8 days[1,2] and of animal malaria by frozen whole blood[4,8] has been reported. It is probable that the reasons for such transmission using whole blood and the lack of transmission using plasma are, first and probably more important, the question of the size of the infecting dose, and second the hemolytic effect of freezing upon the red cell. These reasons would depend upon the assumptions that the vector in this type of malaria transmission was chiefly the parasitized red cell and that no ultramicroscopic form of the plasmodium existed which had thus far escaped detection by the microscopist. The findings in the present study give weight to the validity of these assumptions. It is of interest in this regard that Whitby in a recent review on transfusions remarks that "filtration of plasma or serum offers a complete protection" from the possibility of transmission of malaria.[10] It is assumed that a bacterial filter is meant, and it is regretted that no experimental data are presented. In the present study, no filtration was used in the preparation of the plasma and only a coarse filter sufficient to remove fibrin shreds was used in the administration. With this technique red cells may be detected microscopically in a hanging drop of fresh liquid plasma and red cell "shadows" in a hanging drop of stored liquid or frozen or dried plasma. In connection with the speculation that the parasitized red cell is the probable vector in the transmission, it is of interest to recall the observations made some years ago that in the transmission of therapeutic malaria by small doses of whole blood the injection of incompatible blood resulted in fewer "takes" and longer incubation periods than that of compatible blood.[9,13]

The behavior of the malarial parasite with respect to varying forms of preservation would seem to resemble qualitatively that which has been described by others for the *Treponema pallidum*, which survives preservation in liquid whole blood for 48 hours,[12] and in plasma frozen at $-76°$ C. indefinitely,[11] and in plasma frozen at $-20°$ C. for 24 hours,[10] but not preservation in liquid whole blood for 72 hours[12] or in frozen plasma at $-20°$ C. for 48 hours[10] or in plasma dried from the frozen state.[11]

Summary and Conclusions. 1. Findings on 35 administrations of plasma in dosages varying from 60 to 270 ml. prepared from patients

TABLE 1.—SUMMARY OF RESULTS OF ADMINISTRATIONS TO 35 PATIENTS OF PLASMA PREPARED FROM DONORS WITH ACTIVE MALARIA

Patient	Physical state in which plasma was preserved	Date blood drawn	Date plasma administered	No. of days preservation	Dose in ml.	Type of malarial parasite	No. parasites/ oil immersion field on thick smear donor's blood	Result of injection	Remarks
1	Frozen	7/23/42	7/28/42	5	80	P. malariae	3-4	Neg.	One attempt to infect pt. with whole malarial blood unsuccessful.
2	Frozen	7/23/42	7/28/42	5	80	P. malariae	3-4	Neg.	Pt. came down with malaria 5 days after receiving 5 cc. malarial blood 13 wks. after plasma injection.
3	Frozen	7/28/42	7/28/42	5	80	P. malariae	3-4	Neg.	Pt. came down with malaria 17 days after receiving 5 cc. malarial blood, 12 wks.
4	Frozen	7/28/42	8/4/42	7	160	P. malariae / P. falciparum	30-10	Neg.	Pt. came down with malaria 19 days after receiving plasma injection.
5	Frozen	7/30/42	8/4/42	5	180	P. falciparum	15-20	Neg.	Pt. came down with malaria 19 days after receiving 5 cc. malarial blood, 12 wks. after plasma injection.
6	Frozen	8/7/42	8/10/42	12	80	P. falciparum	4-5	Neg.	
7	Frozen	8/7/42	8/10/42	12	80	P. falciparum	4-5	Neg.	
8	Frozen	8/7/42	8/10/42	12	150	P. malariae	3-4	Neg.	
9	Frozen	9/2/42	9/9/42	7	100	P. falciparum	4-5	Neg.	
10	Frozen	9/2/42	9/9/42	7	100	P. falciparum	4-5	Neg.	
11	Dried	9/7/42	9/9/42	33	100	P. falciparum	4-5	Neg.	
12	Dried	8/7/42	9/9/42	33	150	P. malariae	1-3	Neg.	
13	Dried	9/11/42	9/10/42	33	150	P. malariae	1-3	Neg.	
	Dried	9/11/42	9/10/42	5	80	P. malariae	10-15	Neg.	
	Frozen		11/17/42	31	80	P. malariae	10-15	Neg.	

No.	Plasma	Date	Date			Species		Result	Remarks
19	Frozen	⋮	⋮	34	270	*P. malariæ*	10–15	Neg.	
20	Frozen	10/14/42	11/17/42	36	80	*P. malariæ*	10–15	Neg.	
21	Frozen	10/14/42	11/19/42	28	80	*P. malariæ*	4–5	Neg.	
22	Frozen	10/22/42	11/19/42	28	80	*P. malariæ*	4–5	Neg.	
23	Frozen	10/22/42	11/19/42	28	80	*P. malariæ*	4–5	Neg.	
24	Liquid	11/20/42	11/21/42	1	100	*P. malariæ*	3–4	Pos.!	30 days after injection pt. showed clinical manifestations of malaria and 5–6/para-sites/o.i.f. Required quinine.
25	Liquid	11/20/42	11/21/42	1	60	*P. malariæ*	3–4	Pos.?	28 days after injection pt. showed headache, fever to 100.4° F., no chills and 0–1/para-sites/o.i.f. on 5 occasions. Required no treatment. Same donor as No. 24. Pt. had therapeutic quartan malaria in 1938.
26	Liquid	1/14/43	1/21/43	7	100	*P. malariæ*	6–7	Neg.?	8 wks. after injection pt. showed 0–1/para-sites/o.i.f. on one occasion. No symp-toms. Required no treatment. Pt. had therapeutic quartan malaria in 1933.
27	Liquid	1/14/43	1/21/43	7	100	*P. malariæ*	3–4	Neg.	Same plasma as No. 26 one week older.
28	Liquid	1/14/43	1/21/43	7	100	*P. malariæ*	4–5	Neg.	
29	Liquid	1/14/43	1/21/43	7	100	*P. malariæ*	2–3	Neg.	
30	Liquid	1/14/43	1/21/43	7	100	*P. malariæ*	1–3	Neg.	
31	Liquid	1/14/43	1/21/43	7	100	*P. malariæ*	3–4	Neg.	
32	Liquid	1/14/43	1/28/43	14	100	*P. malariæ*	1–3	Neg.	
33	Liquid	1/14/43	1/28/43	14	100	*P. malariæ*	2–3	Neg.	
34	Liquid	1/14/43	1/28/43	14	100	*P. malariæ*	4–5	Neg.	
35	Liquid	1/14/43	1/28/43	14	100	*P. malariæ*	6–7	Neg.	

with active malaria and preserved by varying techniques for varying periods of time are reported.

2. In 20 administrations of thawed plasma which had been "shell" frozen in a solid carbon dioxide-alcohol bath, no transmissions of malaria were observed.

3. In 3 administrations of restored plasma which had been dried from the frozen state, no transmissions were observed.

4. In 2 administrations of plasma preserved in the liquid state for 1 day, there was 1 definite transmission and 1 probable transmission. In 5 administrations of plasma preserved in the liquid state for 1 week, there was 1 very doubtful transmission. In 5 administrations of plasma preserved in the liquid state for 2 weeks no transmissions were observed.

5. It may be concluded that the likelihood of transmission of malaria by any plasma program, regardless of type of preservation used, is practically non-existent.

REFERENCES

1. ACKERMAN, V., and FILATOV, A.: J. Trop. Med. and Hyg., 37, 49, 1934.
2. ANTSCHELAWITSCH, W. D.: Folia hæmatol., 57, 406, 1937.
3. BOYD, M. F.: Am. J. Trop. Med., 20, 749, 1940.
4. COGGESHALL, L. T.: Proc. Soc. Exp. Biol. and Med., 42, 499, 1939.
5. GARDNER, W. A., and DEXTER, L.: J. Am. Med. Assn., 111, 2473, 1938.
6. GORDON, E. F.: J. Am. Med. Assn., 116, 1200, 1941.
7. JANKELSON, I. R.: J. Am. Med. Assn., 97, 177, 1931.
8. MANWELL, R. D., and JEFFERY, G.: Proc. Soc. Exp. Biol. and Med., 50, 222, 1942.
9. POLAYES, S. H., and DERBY, I. M.: J. Am. Med. Assn., 102, 1126, 1934.
10. RAVITCH, M. M., and CHAMBERS, J. W.: Bull. Johns Hopkins Hosp., 71, 299, 1942.
11. TURNER, T. B., BAUER, J. H., and KLUTH, F. C.: AM. J. MED. SCI., 202, 416, 1941.
12. TURNER, T. B., and DISEKER, T. H.: Bull. Johns Hopkins Hosp., 68, 269, 1941.
13. WENDLBERGER, J.: Wien. klin. Wchnschr., 36, 345, 1927.
14. WHITBY, L. E. H.: Lancet, 1, 581, 1942.
15. WRIGHT, F. H.: J. Pediat., 12, 327, 1938.

THE ACTION OF SPECIFIC STIMULATORS ON THE HEMATOPOIETIC SYSTEM

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THE mechanism of the proliferation and maturation of blood cells is obscure, although assumptions based on the morphology of the blood and blood-forming organs have been made, and something is

known of the action of the anti-anemia factor of liver. Various factors that have been assumed to stimulate and inhibit the growth of blood cells have not been well demonstrated. K. Ziegler,[9] and later Wiseman, Doan, and Erf[8] postulated that a balance was maintained between myeloid and lymphoid tissues. They believed that hyperplasia of the one brought about hypoplasia of the other, but they were unable to explain the mechanism. In previous reports[3,4,5,7] it has been shown that proliferation of lymphoid and myeloid cells can be induced experimentally in guinea-pigs by the injection of specific materials derived from the urines of patients suffering from lymphoid or myeloid leukemia. This work has been confirmed recently by Heinle, and his co-workers.[1] Their results lack uniformity, and this may be ascribed to the lower potency of their material resulting from a less efficient extraction and purification method. The chemical fractionation of our specific stimulating materials has been described elsewhere.[6]

This communication describes the lesions induced in the organs of animals by the administration of our partially purified extracts and fractions of extracts obtained from the urines of patients with acute and chronic lymphoid leukemia, acute and chronic myeloid leukemia, monocytic leukemia, lymphosarcoma, and Hodgkin's disease. Two purposes have been realized, the accumulation of a large series of positive animals and the chemical concentration of the extracts of the active principles; the latter was accomplished by using the biologic test as a criterion of the chemical separation. The specificity of the biologic reaction, which has been emphasized previously, was of great value in the chemical work; it has permitted the collective description of the lesions produced in animals by various fractions that produced the same biologic reactions although obtained at different stages of the chemical concentration.

A theory is proposed concerning the action of the stimulating substances in inducing lesions in animals and the relation of these substances to the formation of similar lesions in some of the human blood dyscrasias.

Materials and Methods. Extracts of urine prepared by a method described in 1940[3] and fractions of these extracts described recently[4,6] were used in the present study.

Guinea-pigs, rats and rabbits have been used. The results have been consistently better in guinea-pigs; however, some of the most marked lymphoid changes have occurred in rabbits and rats. Since spontaneous leukemia is exceedingly rare in the guinea-pig, this animal was chosen for the investigation reported in this paper.

The original chloroform extract, which contained acid and neutral material, was adjusted to pH 7 to 8 with aqueous alkali. Each cubic centimeter of the aqueous solution containing suspended matter corresponded to 1000 to 1500 cc. of urine. It was injected in increasing doses, starting with ¼ cc.; the dose was increased every 5 days until 1½ or 2 cc. was given daily. The first fractions obtained by the chemical separation of this extract were given either undiluted or in olive or sesame oil in 3 to 4 doses of 50 to 400 mg. per dose which represented similar or slightly greater amounts of urine. Subsequent fractions usually have been given undiluted. The doses of these fractions have been adjusted to permit a comparison of the two fractions produced by each procedure in the separation. Thus, when two fractions were obtained with 10

times as much material in one as in the other, these proportions were maintained in the amounts given of each part.

Blood counts of the animals were not of special significance. Most of the myeloid animals had some anemia and leukocyte counts of 40,000 to 50,000 were obtained several times. The hemograms of the lymphoid and myeloid animals were usually different. In the former, although the total leukocyte counts were normal, relative lymphocytoses occurred. In the latter, myelocytes, myeloblasts, and nucleated erythrocytes frequently appeared in the peripheral blood. The animals were killed as soon as they became moribund. This usually occurred 3 to 5 weeks after the beginning of the experiment. Most of the animals at necropsy were found to have necrosis and hemorrhage at the sites of injection. This occurred in negative as well as in positive animals.

Description of the Induced Lesions.* Thirty-six animals have been given the active principle, either as extracts or as fractions of extracts from the urine of patients with *chronic myeloid leukemia*. All these animals have exhibited changes in their organs similar to the changes of human chronic myeloid leukemia. Liver, spleens, adrenals, and bone marrows have shown myeloid proliferation invariably; the lungs, kidneys, and lymph nodes have been affected less frequently. In the liver, metaplasias of young erythroid and leukoplastic cells were found between the liver cords, around blood-vessels, and to some extent in periportal areas. Megakaryocytes occurred frequently in this new growth of young blood cells. The architecture of the spleen was disarranged because of the presence of myeloid proliferation, and a lack of lymphopoiesis was evident. In the adrenal, the metaplastic myelopoiesis has occurred under the capsule and in the cortex; less frequently, it has been noted in the medulla. In the cortex it has occurred as nests of forming cells between the cords or intravascularly. The bone marrows of all these animals have been hyperplastic in all the cellular elements (Figs. 1, 2).

Three animals have received the extracts of the urine from 2 patients with *acute myeloid leukemia*. The changes in the organs of these animals were exactly similar to those in the animals that received material from the urine of patients with chronic myeloid leukemia. The acute nature of the disease was not transferred (Fig. 3).

Forty animals received the lymphoid stimulating substance either as extracts or as fractions of extracts of the urine from patients with *chronic lymphoid leukemia*. These exhibited changes similar to those found in human chronic lymphoid leukemia. There was much less liver involvement than in animals that received myeloid substance, and this occurred as perivascular infiltrations or as minute lymph nodes. The spleens were always hyperplastic in cellular contents, often showing merely enlargement or increased numbers of lymph follicles; at times, however, the hyperplasia obliterated the entire splenic architecture. All the lymph nodes were somewhat enlarged and rupture of the capsule was noted several times. The kidneys were more often involved than in our myeloid animals. In animals that received the

* The accompanying photomicrographs represent sections of the organs of guinea-pigs, and illustrate the lesions produced by the active material obtained from various urines. The urinary source is indicated briefly following the identification of the organ. All sections were stained with hematoxylin and cosin.

lymphoid stimulating substance, the adrenals were less frequently involved than in animals that received myeloid stimulating substance, and when involvement occurred it manifested itself in the medulla rather than under the capsule or in the cortex (Figs. 4, 5).
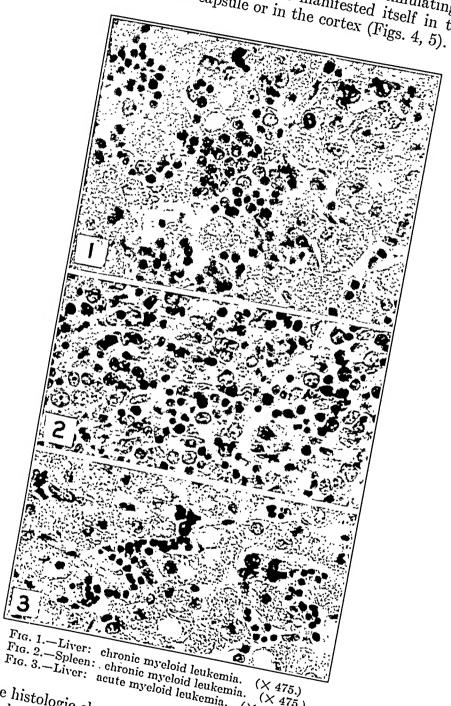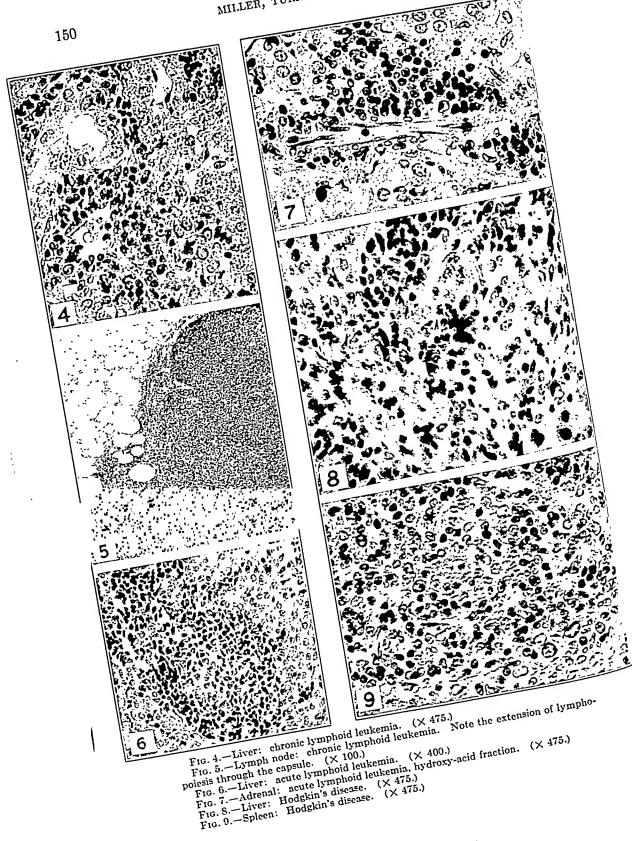
FIG. 1.—Liver: chronic myeloid leukemia.   (× 475.)
FIG. 2.—Spleen: chronic myeloid leukemia.   (× 475.)
FIG. 3.—Liver: acute myeloid leukemia.   (× 400.)

These same histologic changes were obtained in 8 animals given the active principle from the urine of 4 patients with acute lymphoid leukemia, although the lymphoid hyperplasia and metaplasia in non-lymphoid organs were somewhat greater than that elicited by chronic lymphoid extracts (Figs. 6, 7).

Fig. 4.—Liver: chronic lymphoid leukemia. (× 475.)
Fig. 5.—Lymph node: chronic lymphoid leukemia. Note the extension of lympho-
poiesis through the capsule. (× 100.)
Fig. 6.—Liver: acute lymphoid leukemia. (× 400.)
Fig. 7.—Adrenal: acute lymphoid leukemia, hydroxy-acid fraction. (× 475.)
Fig. S.—Liver: Hodgkin's disease. (× 475.)
Fig. 9.—Spleen: Hodgkin's disease. (× 475.)

FIG. 10.—Trachea: Hodgkin's disease. Note the infiltration in tissue between cartilage. (× 100.)

FIG. 11.—Spleen: Hodgkin's disease, hydroxy-acid fraction, showing lymphoid hyperplasia. (× 475.)

FIG. 12.—Lymph node: Hodgkin's disease, hydroxy-acid fraction, showing lymphoid hyperplasia. (× 475.)

Again, to a lesser degree, lymphoid hyperplasia and pictures simulating lymphoid leukemia were obtained in 8 animals after the use of the partially purified extracts of urine from 4 patients with *lymphosarcoma*.

Four animals were given the partially purified extract of the urine from 2 patients with *monocytic leukemia*. The changes elicited in the organs of these animals were neither lymphoid nor myeloid. The liver showed some perivascular infiltration with small round cells similar to lymphocytes, and at times this infiltration contained many eosinophils. The liver of 1 animal showed minute nodules composed of round cells, eosinophils, and fibroblasts. The spleens contained many large cells with foamy cytoplasm, many fibroblasts, and a few multinucleated giant cells. The lymph nodes were somewhat enlarged in all these animals and the histologic changes were similar to the changes in the spleens. All the bone marrows were hyperplastic, and there was always
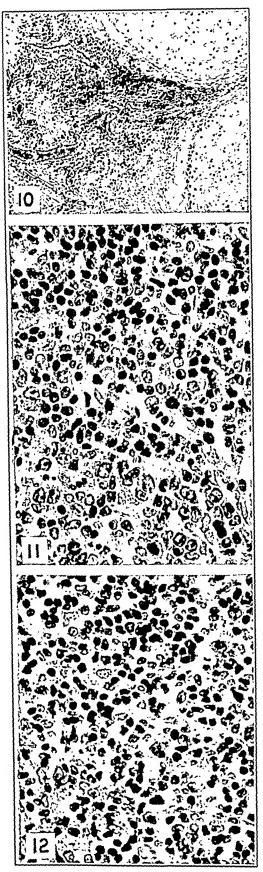

FIG. 13.—Lymph nodes surrounding trachea: chronic myeloid leukemia, hydroxy-acid fraction, showing lymphoid hypertrophy.   ($\times$ 8.)

an increased number of megakaryocytes. In all these lesions the number of mitotic figures also was increased.

The same changes occurred in the organs of 6 animals treated with similar material from 2 patients with Hodgkin's disease. In these, however, a more definite trend towards lymphoid stimulation was apparent. In 2 animals, the lymph nodes had the appearance of lymphosarcoma with proliferation of cells through the capsules and, in one instance, the nodes found near the trachea showed infiltration between the cartilages of this organ. Again, there was an increased number of mitotic figures in the lesions (Figs. 8, 9, 10).

Each of 3 animals was given equal weights of lymphoid and myeloid stimulating fractions simultaneously. These fractions were both obtained at a similar stage of the fractionation procedure described elsewhere[6] and corresponded to acids B of that paper. The changes in the histology of the organs of these animals resembled the changes
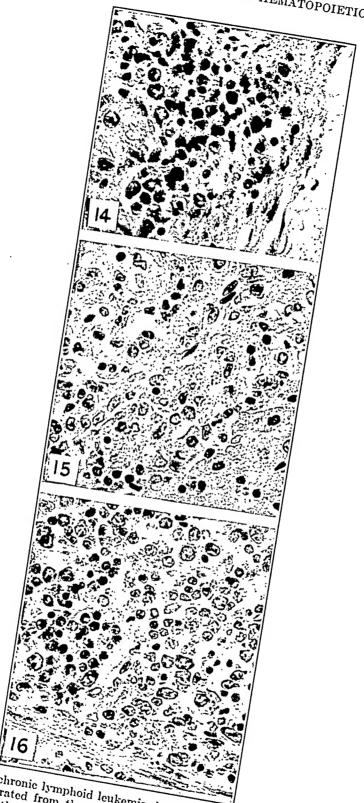
Fig. 14.—Adrenal: chronic lymphoid leukemia, hydroxy-acid fraction oxidized and non-carbinol acids separated from the product and injected. This shows a myeloid reaction beneath and in the capsule. (× 475.)

Fig. 15.—Liver: chronic lymphoid leukemia, non-carbinol acid fraction. Note the myeloid reaction between liver cords. (× 475.)

Fig. 16.—Spleen: chronic lymphoid leukemia, non-carbinol acid fraction. Note the erythropoiesis and myelopoiesis. (× 475.)

found in the animals that received extracts of the urine of patients with Hodgkin's disease or monocytic leukemia.
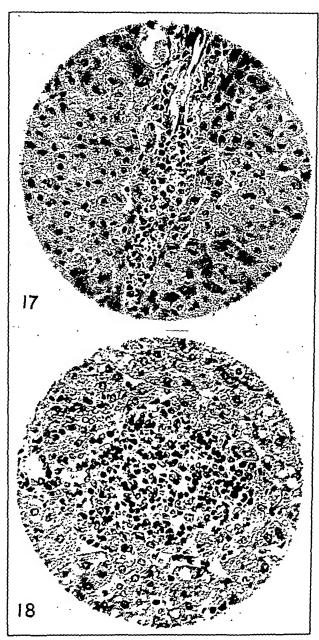
Fig. 17.—Liver: injection of equal weights of myeloid and lymphoid stimulating fractions. This shows perivascular lymphoid infiltration accompanied by eosinophils. (× 475.)

Fig. 18.—Liver: monocytic leukemia, non-carbinol acid fraction reduced and hydroxy-acids separated from the product and injected. This shows a lymphoid reaction. (× 475.)

In our paper describing the chemical aspects of this problem[6] it has been shown that mixtures of the myeloid stimulating substance and the lymphoid stimulating substance can be separated. The lymphoid stimulating material was removed from the mixture in the fraction containing hydroxy-acids, while the myeloid stimulating material remained with the non-carbinol acids. By employing this procedure it was possible to show the presence of small amounts of lymphoid stimulating material together with large amounts of myeloid stimulating material in the urine of patients with chronic myeloid leukemia.
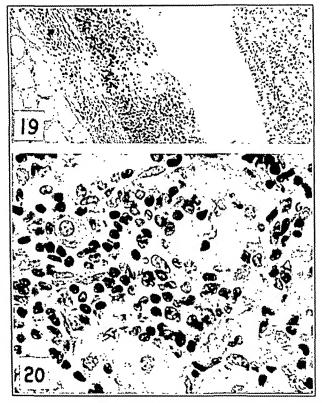
FIG. 19.—Pelvis of kidney: same material as Figure 18. (× 100.)
FIG. 20.—Medulla of adrenal: same material as Figure 18. (× 475.)

The urine of patients with monocytic leukemia or Hodgkin's disease was found to contain the two specific myeloid or lymphoid stimulating substances in a more equal proportion. The mixtures were separated in the same manner and the hydroxy-acid fraction gave a pure lymphoid response in animals while the non-carbinol acids gave a pure myeloid picture in animals.

The urine of patients with chronic lymphoid leukemia was shown to contain small amounts of myeloid stimulating material besides large amounts of lymphoid stimulating material.

No myeloid stimulating substance was found in the urine of 2 patients with acute lymphoid leukemia.

The biologic results supporting these chemical separations are shown

in Chart 1. The degree of activity of each fraction is also noted in Chart 1.

CHART 1,—ACTIVITY OF CHEMICAL FRACTIONS

Material	Myeloid leukemia		Lymphoid leukemia		Monocytic leukemia	Hodgkin's disease
	Chronic	Acute*	Chronic	Acute		
Hydroxy-acids:						
Lymphoid activity	+ (2)	— (2)	+++ (2)	+++ (2)	++ (2)	+++ (2)
Non-carbinol acids:						
Myeloid activity	+++ (2)	++ (2)	+ (2)	— (2)	+++ (2)	++ (4)

* Since the manuscript was sent to press, one urine of a patient with acute myeloid leukemia has become available and the result entered on this chart.
The number of animals employed is indicated in parentheses.
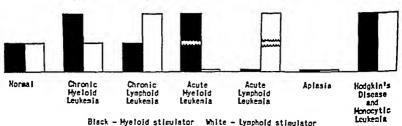
In the same report,[6] a chemical method was described for the conversion of the lymphoid stimulating substance to myeloid stimulating material. The reverse transformation was accomplished also. This involved a reduction for the conversion of myeloid material to lymphoid and an oxidation for the reverse change. These reactions in each instance were applied to material containing only one of the two biologically active substances (Figs. 11 to 20).

Discussion. The chemical evidence reported elsewhere[6] suggests strongly that there are only 2 substances involved in producing the specific histologic changes described in this paper, although a variety of urinary sources has been used. These substances, one of which produces myeloid proliferation, and the other lymphoid, are closely related chemically.

In order to explain the action of the 2 substances we have formulated a theory which accounts in part for their physiologic activity.

In the amounts we have used, no active material has been found in the urine from normal individuals. We assume, however, that the body fluids of normal individuals must contain similar substances and that normal hematopoiesis is regulated by them. On this assumption and from our findings we have charted in a rough way the occurrence of these substances in the normal and in several of the blood dyscrasias (Chart 2).

CHART 2.—THEORETICAL OCCURRENCE OF STIMULATING SUBSTANCES IN THE NORMAL AND SEVERAL OF THE BLOOD DYSCRASIAS

Black – Myeloid stimulator   White – Lymphoid stimulator

We suggest that these substances are mutually reciprocal in action. The myeloid substance stimulates myelopoiesis, i. e., proliferation

without maturation. The maturation of myeloid cells is brought about by the action of the lymphoid substance which inhibits the proliferation of the myeloid cells and hence allows them to mature. The lymphoid substance brings about lymphoid proliferation without maturation. Maturation of these cells is brought about by the action of the myeloid substance which inhibits the proliferation of the lymphoid cells and hence allows them to mature. Normally, the 2 substances are balanced in action and therefore regulated hematopoiesis occurs. We postulate that an excess of myeloid substance occurs in chronic myeloid leukemia together with at least a normal amount of lymphoid substance. Hence the disease runs its course with greater than normal maturation of myeloid cells in evidence. As the lymphoid substance becomes exhausted, an acute exacerbation occurs, characterized by proliferation of myeloid cells without maturation. Death follows with the disease in an acute or blastic phase. Chronic lymphoid leukemia may be explained in a similar manner.

The two acute diseases, acute lymphoid and acute myeloid leukemia, may be explained as deficiencies of one or the other maturating substance.

By giving lymphoid or myeloid substance to animals we have experimentally reproduced the two diseases in which an excess of one substance and at least a normal amount of the other are assumed to occur. The detection of both substances in the urines of patients with these two diseases substantiates this assumption, and also explains the inability to reproduce the acute phases of these diseases. If one or the other substance could be destroyed or removed from the animals the corresponding deficiency disease easily would be obtained. In the extracts of urine of 2 patients with acute lymphoid leukemia we were unable to demonstrate myeloid substance. Theoretically, we should not obtain more than one substance from the urines of patients in the acute phase of leukemia.

Hypoplastic or aplastic anemia may be assumed to be a deficiency disease in which both factors are lacking; therefore, little proliferation and little maturation of either type of cell takes place.

We have found both stimulating substances in excess in the urine from patients with Hodgkin's disease and monocytic leukemia; therefore we have placed these two diseases in that category on Chart 2. The reaction observed in the animals that received both substances substantiates this part of the hypothesis. Lymphosarcoma is omitted from the chart, but from this work it would seem to be a variation of lymphoid leukemia.

This work may lead to a new type of therapy for human leukemia.[2] If the theory is correct, leukemia resulting from a lack of one of the 2 substances may be controlled by the replacement of this substance. The theory, however, implies that such replacement therapy would be useful in the chronic leukemias only in preventing the occurrence of acute or blastic phases.

Summary. Descriptions and photomicrographs are given of lesions observed in animals following injection of 2 substances obtained from

urines of patients with leukemia, and allied diseases. A theory is proposed to account for the action of these substances. This work may provide a basis for a better understanding of leukemia and of normal hematopoiesis.

REFERENCES

1. HEINLE, R. W., WEARN, J. T., WEIR, D. R., and ROSE, F. A.: Ann. Int. Med., 17, 902, 1942.
2. JONES, H. W., MILLER, F. R., and HAUSE, W. A.: Trans. Assn. Am. Phys., 45, 54, 1940.
3. MILLER, F. R., and HAUSE, W. A.: Proc. Soc. Exp. Biol. and Med., 45, 387, 1940.
4. MILLER, F. R., HAUSE, W. A., and JONES, H. W.: Proc. Soc. Exp. Biol. and Med., 50, 115, 1942.
5. MILLER, F. R., WEARN, J. T., and HEINLE, R. W.: Proc. Soc. Exp. Biol. and Med., 41, 479, 1939.
6. TURNER, D. L., and MILLER, F. R.: J. Biol. Chem., 147, 573, 1943.
7. WEARN, J. T., MILLER, F. R., and HEINLE, R. W.: Trans. Assn. Am. Phys., 54, 278, 1939.
8. WISEMAN, B. K., DOAN, C. A., and ERF, L. A.: J. Am. Med. Assn., 106, 609, 1936.
9. ZIEGLER, K.: Experimentelle und klinische Untersuchungen über die Histogenese der myeloischen Leukämie, Jena, G. Fischer, 1906.

SICKLING TRAIT IN A WHITE ADULT ASSOCIATED WITH HEMOLYTIC ANEMIA, ENDOCARDITIS AND MALIGNANCY*

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UNTIL Cooley and Lee[3] first reported an authenic case of sickle-cell anemia in a white person, the disease was assumed to be characteristically one of the negro race. Additional trustworthy cases[1-6,8,8a,10-14,17] have subsequently accumulated; the pertinent data of the known cases are summarized in Table 1. It seems more than a coincidence that these, and the patient to be reported, are all of South Italian stock. The not infrequent occurrence of the sickle-cell trait in Puerto Ricans and Mexicans is understandable, because of the high incidence of cross-breeding with the negro race. In tracing the derivation of those patients whose family history admits of no such admixture, one is struck by the high proportion with Mediterranean background.

It is a moot question, whether, as some students of the disease predicate, a negro strain was introduced during the migrations and wars of ancient or even earlier times, or whether the sickle-cell trait need not

carry any connotation of negro heritage. The subject has more than ethnologic or historic interest, for it may be a clue to the diagnosis and understanding of a hitherto bizarre and unrecognized group of hemolytic anemias. For this reason, it is suggested that the blood in all cases of obscure hemolytic anemia be tested for the sickling trait.

An additional case of hemolytic anemia in a white person who showed the sickling trait and in whom a metastatic carcinoma was found on postmortem examination, is presented in this communication.

TABLE 1.—RÉSUMÉ OF PREVIOUS REPORTED CASES OF SICKLE-CELL ANEMIA IN WHITE PERSONS

Author	Year	Age	Sex	Birth-place	Father's birthplace	Father's blood	Mother's birthplace	Mother's blood	Remarks
Cooley and Lee[3]	1929 1929	4 yrs. 14 yrs.	M M	U. S. U. S.	Byregos, Greece	Normal	Byregos, Greece	Sickles	2 siblings, normal
Sights and Simon[12]	1931	48 yrs.	M	U. S.	U. S.	Not exam.	U. S.	Not exam.	Patient had lues and malaria, transient sickling; Scotch-Irish descent
Rosenfeld and Pincus[11]	1932	9 yrs.	M	U. S.	Reggio, Calabria, So. Italy	Normal	U. S., parents from Casabana, Calabria	Sickles, long-standing anemia	Maternal grandmother and aunt and 1 sibling sickle
Clarke[1]	1933	3 yrs. 11 yrs.	M M	U. S. U. S.	Carlentina, Sicily	Normal	Carlentina	Normal	3 siblings, normal
Cooke and Mack[2]	1934	10 mos. 3½ yrs.	M F	U. S.	U. S. (Ohio)	Sickles	U. S., parents from Ky., Va.	Normal	4 siblings have palpable spleen, no sickling
Haden and Evans[5]	1937	8 yrs. 15 yrs.	F F	Sicily U. S.	Sicily	Died of blood dyscrasia atypical anemia	Sicily	Normal	1 brother sickles, 4 siblings normal
Johnson and Townsend[6]	1937	5 yrs.	M	Greek	Greece	Dead	Greece	Normal	3 siblings not examined
Weiner[17]	1937	8 yrs.	M M	U. S. N. J.	Mistressa, Sicily	Normal	Mistressa, Sicily	Normal	Maternal grandmother neg., 1 sister neg., 2 younger brothers show anemia, sickling and splenomeg.
Pontoni[10]	1939	13 yrs.	F	Italy					Quotes 2 cases previously reported in the Italian literature
Greenwald and Burrett[4]	1940	22 yrs. 9 yrs.	F F	U. S. U. S.	Naro, Sicily	Not exam. dead	Naro, Sicily	Sickles	Mother, aunt and cousin sickle
Mallory[8,8a]	1941	20 yrs.	F	U. S. Boston	Italy	Refused exam.	Italy	Normal	2 siblings negative
Wade and Stevenson[14]	1941	49 yrs.	F	Greek					No familial history
Vance and Fisher[13]	1941		M		Greek parentage				No additional family history

Case Study. L. D., admitted on Aug. 13, 1941. Female, white, age 54; born in Palmerno, Italy.

Present History. Weakness, fever, generalized aches and pains and head-ache were first noted on August 3, and became progressively worse. A "black-eye" and several other areas of ecchymoses were noted 2 days before admission.

Family and Past History. The patient was an adopted child and nothing is known of her parents, though they came from the same village as her foster parents, where negroes were unknown. She is said to have had no siblings. She had enjoyed reasonably good health. Para vii; 6 children are alive and well. One daughter died of hemorrhage following childbirth. Menopause was uneventful two years ago. The patient was operated upon in March 1941, when a cholecystectomy was performed because of a phlegmonous gall bladder.

Physical Examination.—On admission the patient was extremely ill, temperature 101.6° F., pulse 80 to 120, respiration 20 to 30. She was pale and jaundiced, obese, and there were no negroid features. There was a periorbital ecchymosis of the right eye, and a few scattered petechiæ and ecchymoses. Tachycardia was noted, and there was a blowing systolic murmur heard best over the pulmonic area; blood pressure 112/55. The lungs were clear. The abdomen was soft and not tender. The liver and spleen were not felt. A transverse scar was noted in the right upper quadrant. There was no peripheral edema, and reflexes were normal.
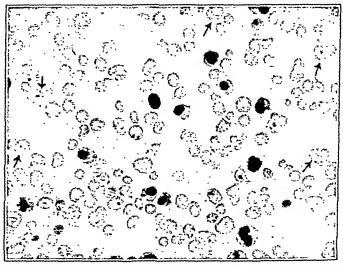
FIG. 1.—Peripheral blood smear showing erythroblastosis and target cells (some are marked by arrows). (× 1350.)

Laboratory Data. Peripheral blood count the day following admission: Hgb. 25%, R.B.C. 1.30 million, W.B.C. 26,000; differential: myeloblasts 2%, neutrophilic myelocytes 3%, metamyelocytes 6%, staff forms 30%, segments 25%, eosinophils, 3%, lymphocytes 30%, monocytes 1%, normoblasts 55 and erythroblasts 5 per 100 W.B.C. (Fig. 1), reticulocytes 17.6%, R.B.C. showed slight anisocytosis, hyperchromia and polychromasia. There was slight poikilocytosis. The bone marrow (aspiration) was hyperplastic and erythroblastic, with good distribution of the myeloid elements. Few megakaryocytes were seen (Fig. 2). Platelet count: 60,000 platelets, which dropped in 5 days to 15,000. Subsequent blood counts are recorded in Table 2. Coagulation time was 3¼ minutes; bleeding time, 2¼ minutes. Clot retraction began in 1 hour and was complete in 15 hours. The tourniquet test was positive. Hemolysis to hypotonic saline began at 0.495 and was complete at 0.270. Icteric index was 28 on admission and rose to 80, with a positive immediate

direct Vandenburg reaction. Sickling of the R.B.C. in a "wet-slip prepara-
tion" was demonstrated on several occasions (Fig. 3). Blood chemical figures
per 100 cc. of blood were: N.P.N. 25 mg., glucose 130 mg., total cholesterol
180 mg., cholesterol esters 68 mg., creatinine 1.5 mg., total protein 7.83 gm.;
albumin, 4.64 gm., globulin 2.89 gm., fibrinogen 0.3 gm., prothrombin index
78%; gastric analysis free acid absent after histamine. The urine showed no
hemoglobinuria. Roentgen ray of chest (Aug. 14, 1941) "the transverse diameter
of the heart shadow is somewhat increased. The hilar and parenchymal mark-
ing are increased. Impression: cardiovascular disease." E.C.G. (Aug. 14,
1941): "Q_1 absent, T_1 low. Left axis deviation. Impression: possible myo-
cardial damage."
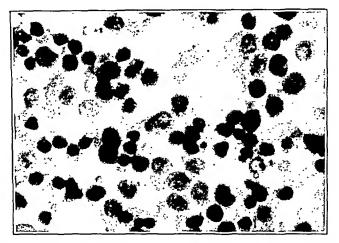
Fig. 2.—Sternal marrow smears showing hyperplastic erythro-normoblastic marrow.
($\times$ 1350.)

Fig. 3.—Wet preparation showing marked sickling of erythrocytes. ($\times$ 1350.)

Course. Frequently repeated blood transfusions (9 in all), large doses of
cevitamic acid and parenteral liver extract had little effect upon the clinical
course or upon the blood picture. The patient died on August 30, 1941.

Necropsy. GROSS (Dr. Andrea Saccone, of Metropolitan Hospital): *Heart.*
450 gm. The apex is covered with a slight amount of yellow fat. The right
ventricular wall measures 5 mm. in thickness, the left, 1 cm. On the corpora
Arantii there are some very fine vegetations. The same type of vegetations

is present on the mitral valve.   There is no change in the tricuspid valve.
The foramen ovale is closed.   The myocardium is uniformly dull in appear-
ance, but there are some grayish areas in the myocardium supplied by the
anterior descending coronary artery.   The circumflex (left) coronary artery on
section shows only some patches of sclerosis.   The aorta has a reddish-yellow
intima and, starting at the arch, there are some patches which are raised.

Respiratory Apparatus.   The larynx, trachea and large bronchi are covered
with a slight amount of yellowish mucus.   The glands at the hilus of the lung
are small, discrete and dark in color.   The left lung weighs 450 gm.   It is slightly
yellowish in color with small areas of atelectasis.   There is a small area of
atelectasis, with its base, measuring 1 cm., at the lower edge of the lung.
Large amounts of foamy fluid can be expressed from the lung.   The right lung
weighs 550 gm.   The lower lobe is dark red in color and firm.   On section it
has the same appearance as the left lung.
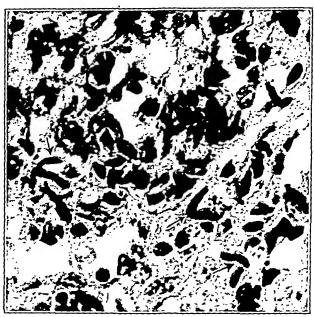
Fig. 4.—Spleen showing sickle-cells (arrows) in pulp spaces near a trabecula.
(× 1125.)

Spleen.   180 gm.   The capsule is tense and at the edge of the capsule there
are some dark areas which are sharply demarcated on section.   The pulp is
firm with prominent trabeculæ.

Pancreas.   180 gm.   There is an increase of the connective tissue on section.

HISTOLOGIC (Dr. F. D. Speer): *Spleen* (Fig. 4) shows moderate congestion.
The capsule and trabeculæ show a slight increase in fibrillar connective tissue.
Small and moderate sized collections of lymphoid tissue are noted about the
splenic arterioles.   No active "germinal centers" are seen.   The arterioles them-
selves show slight thickening of their walls due to an increase of fine fibrillar
connective tissue.   High-power study of the splenic pulp shows a moderate
number of elongated and sickle-shaped red blood cells throughout.   It is esti-
mated that this cell type comprises about 10% to 15% of the red cells seen in
the pulp.   There is no apparent increase in leukocytes or in splenocytes in the
pulp.   Another section of the spleen shows a small triangular-shaped sub-
capsular area in which the finer pulp structures shows slight granular disinte-
gration.   Immediately beneath the capsule there is a narrow zone of congestion
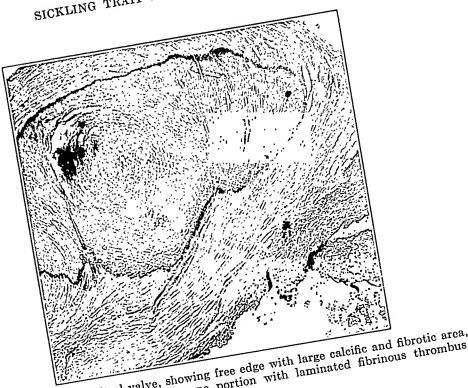
FIG. 5.—Part of mitral valve, showing free edge with large calcific and fibrotic area, endothelial surface destroyed over one portion with laminated fibrinous thrombus. (× 175.)
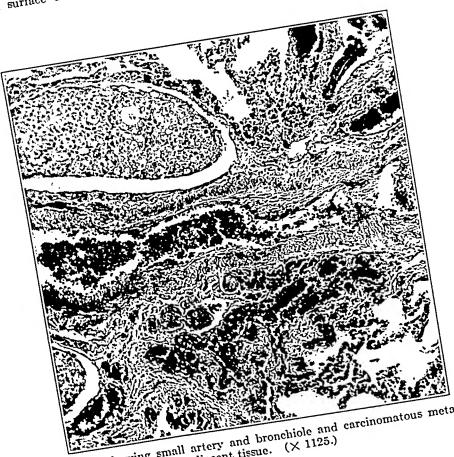
FIG. 6.—Lung showing small artery and bronchiole and carcinomatous metastasis in adjacent tissue.   (× 1125.)

and hemorrhage. Throughout this zone, and also throughout the pulp tissue, there is a number of small blood-vessels occluded by thrombi in which fibrin and a few red and white blood cells can be identified. There is also an extensive zone of congestion and hemorrhage in the pulp and adjacent to the area of granular necrosis. In these areas of congestion and hemorrhage, small numbers of sickle-shaped red blood cells are seen.

Pathologic Diagnosis. Fibrosis, moderate congestion, moderate numbers of sickle-shaped red cells in pulp, small recent infarct showing adjacent hemorrhage, focal thrombosis of the smaller blood-vessels.

Mitral Valve (Fig. 5) shows a pyramidal segment of myocardial muscular tissue at the base. The valve leaflet shows a minimal increase in hyalinized connective tissue. At the edge of the valve there is a large knoblike thickening consisting of laminated hyalinized connective tissue and a calcified center. The surface of the valve covering this nodule shows an irregularly shaped thrombotic mass consisting essentially of old fibrin in which there are a few entrapped red blood cells and leukocytes. No bacterial colonies are demonstrated in this thrombotic mass. In this section of valve and attached myocardium there are no Aschoff lesions.

Pathologic Diagnosis. Focal fibrosis and calcification (healed rheumatic valvulitis). Small valvular thrombi consisting of old fibrin (thromboendocarditis).

Liver. Central albuminous and fatty degeneration and cytonecrosis, focal fatty infiltration, periportal fibrosis, focal fibrin thrombi in sinusoids, isolated sickle-shaped red blood cells.

Lungs (Fig. 6). Focal atelectasis and edema, multiple small carcinomatous metastases (bronchogenic origin?).

Peritracheal Lymph Nodes. Anthracosis, metastatic anaplastic carcinoma (bronchogenic origin?).

Pancreas. Slight peripancreatic fibrosis, minute carcinomatous metastases in peripancreatic tissues. Multiple carcinomatous metastases and fibrosis of lymph nodes.

TABLE 2.—BLOOD FINDINGS OF THE PATIENT

Date	Hgb. (%)	R.B.C.	W.B.C.	Platelets	Myeloblasts	Myelocytes	Metamyelocytes	Stab	Segmented	Lymphocytes	Monocytes	Eosinophils	Reticulocytes (%)	Nucleated R.B.C.	Morphology
8/14	25	1.30	26,000		2	3	6	30	25	30	1	3	17.6	60	Aniso. macro. microcytosis, polychromasia, hyperchromia, occasional sickle cells, target cells
8/18	25	1.25	36,300	60,000											"
8/20	25	1.45	24,100		1	2	8	16	40	30		3	21.0	157	"
8/23	25	1 53	30,300												"
8/25						3	11	16	37	28	3	2	19.2	95	"
8/26	22	1.18	30,800	15,000											"
8/28					1	5	11	14	26	36	2	5	20 0	133	"

Following the recognition of sickling of the erythrocytes in the patient all of her descendants were examined for the sickle-cell trait. Latent sicklemia was demonstrated in 4 members of the family: 2 sons. a daughter and a grandchild (see Chart 1). They are all well and give no history suggestive of previous hemolytic crises nor show any hematologic evidence at present, of active disease (Table 3). It will be noted that an increased fragility to hypotonic saline was found in 3 of these cases, as well as in the patient. This is contrary to the usual finding of increased resistance.

Discussion. There are several points of interest in the above story. The advanced age of the patient, the finding of malignancy and the rela-

tionship of this finding to the differential diagnosis of the anemia, the endocardial lesion demonstrated, and the associated thrombocytopenia are all unusual and deserving of some comment.
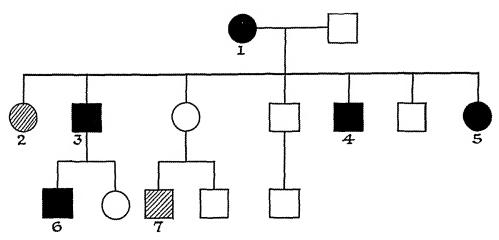
CHART 1.—Black circles (females), rectangles (males) indicate those who showed sickling of erythrocytes. (1) The patient; (3, 4, 5) her two sons and daughter; (6) a grandson; (2) daughter died of hemorrhage at childbirth; (7) grandchild died of pneumonia at the age of 1 year.

TABLE 3.—BLOOD FINDINGS IN THE DESCENDANTS SHOWING THE SICKLE-CELL TRAIT

Name	Sex	Age (yrs.)	Hgb. (%)	R.B.C.	W.B.C.	Platelets	Reticulocytes (%)	Stab	Segmented	Eosinophils	Lymphocytes	Monocytes	Fragility, R.B.C.	Icteric index	Wassermann	Morphology
F. D.	M	36	95	4.95	7,800	230,000	0.2	3	69	1	25	2				Normal red cells
L. D.	M	28	100	5.06	8,800	350,000	0.2	1	58		35	6	0.52 to 0.32	4	Neg.	Rare target cell
A. D.	F	23	81	4.40	6,200	340,000	0.2	3	57	3	30	7	0.52 to 0.32	6	Neg.	Rare target cell, rare sickle cell
F. D., Jr.	M	12	76	4.45	6,000	300,000	0.4		49	3	38	10	0.48 to 0.32		Neg.	Slight anisocytosis, rare target cell

This is the oldest in the group of non-negro patients collected in Table 1. With the exception of Wade and Stevenson's[14] 49 year old patient, and Sights and Simon's[12] 48 year old patient (which has been included but not definitely accepted), the patients were all in the first or second decades of life. Nothing in our patient's history suggested any hemolytic crisis before the fatal one at 54 years of age. Although sickle-cell anemia usually begins in childhood, the first symptoms of the disease have been observed in a negro 78 years old.[18] No iron deposition was found in the liver nor in the cells of the reticuloendothelial system. The moderate fibrosis of the spleen, as noted, is the only suggestion that earlier mild episodes of hemolysis may have taken place.

Clinically and hematologically the findings associated with a hemolytic crisis dominated the picture, viz., anemia, icterus, reticulocytosis,

macrocytosis and normoblastosis. The thrombocytopenia and hemorrhagic diathesis are unusual, but have been reported.[9] The etiologic factor accounting for the acute hemolytic episode was obscure until illuminated by the demonstration of the sickling trait. Differential diagnosis suggested several possibilities. Cancer, ultimately found by microscopic examination of the organs, though considered, could not be demonstrated clinically, and the patient was too ill to be subjected to rigorous diagnostic procedures. Acute hemolytic anemia of the so-called "Lederer" type was a tentative diagnosis. Failure to respond to repeated transfusion tended to remove her from this group. The indication for splenectomy was considered in view of the lack of response to transfusions, but discarded because of the discovery of sickling and the critical condition of the patient. Bone marrow studies ruled out a possible leukemia, suggested by the leukemoid peripheral white cell response. A careful search into her dietary habits failed to confirm favism as a possibility. No history of drugs nor contact with cyclic chemicals could be obtained.

Before the necropsy report, the case obviously appeared to be one of sickle-cell anemia in crisis. The postmortem findings of metastatic carcinoma and an endocardial lesion offered two additional possible causes for the hemolytic crisis. Any of these conditions may have produced this type of anemia. The absence of bacterial growth on the endocardial lesion and the necropsy findings tended to rule out infection as the cause of the anemia. Unfortunately no blood culture was done. There are several observations which incline toward the view that hemolysis was secondary to sicklemia rather than to malignancy. *A.* Sickle cells were demonstrated in the spleen, liver and in the heart's blood postmortem. It is accepted that actual sickling of cells within the internal organs occurs only in the active phase of the disease, whereas in latent cases, *in vitro* lowering of oxygen tension is necessary, to produce sickling. *B.* The malignant lesions were small, subclinical, found only on histologic sections and metastasis were apparently limited to the lymph drainage areas in the lungs, peritracheal lymph nodes, peripancreatic tissue and lymph nodes. Repeated search of bone marrow material failed to disclose any cells suspicious of malignant characteristics. Though reported,[16] hemolytic anemia due to malignancy is admittedly quite rare. Waugh's[16] cases showed extensive metastasis to the bones, either by Roentgen ray or direct examination. *C.* The violently acute onset of the clinical course, its rapid downhill progress, and the domination of the picture by the hemolytic anemia syndrome seem to be more in favor of sickling as the etiology. *D.* And finally, the moderate amount of splenic fibrosis found suggests one or more previous unrecognized episodes of mild hemolysis. Fragility to hypotonic saline was somewhat increased. This is more concordant with Waugh's observations in 2 cases of malignancy with hemolytic anemia and with one similar case seen by the writers. Sickle-cell anemia, on the other hand, is usually associated with increased cell resistance. It should be noted, however, that increased fragility was found in 3 of the patient's descendants who showed sicklemia.

The endocardial lesions were described as focal fibrosis and calcification of the mitral valve (healed rheumatic valvulitis). No previous history suggestive of rheumatic fever had been obtained. Although the similarity between manifestations of acute crisis of sickle-cell anemia and rheumatic fever have been pointed out repeatedly, and the diagnosis of rheumatic fever has been made mistakenly many times, the literature contains only 1 case[15] of both diseases coexisting. Klinefelter,[7] writing recently, but probably before Walker and Murphy's[15] case was published, gives an excellent résumé of the heart in sickle-cell anemia and stresses that "although the diagnosis of rheumatic heart disease has often been made in patients with sickle-cell anemia, it has not been confirmed at autopsy." In our case, the lesion, unsuspected during life, was a chance postmortem observation.

Though thrombocytopenia and hemorrhagic diathesis may occur in either sickle-cell anemia or metastatic carcinoma, its presence is noted again as unusual.

The possibility of sickle-cell anemia in all cases of obscure hemolytic anemia regardless of race should be borne in mind. While rarer in whites than in negroes, this disease may be more common than supposed, and may be overlooked because it is not customary to examine wet-sealed blood preparations routinely. It should be noted that, through the cases reported and summarized here, additional blood relatives, unsuspectingly bearing the trait, have been revealed. Any of these may, in the future, become active cases. Undoubtedly, many others showing sicklemia would be found if wide-range examinations of ethnic groups other than negroes were done, especially among Mediterranean peoples.

Parallelism between erythroblastic anemia of Cooley and sickle-cell anemia has been pointed out by many. Both conditions are basically congenital defects of the red corpuscle occurring predominantly in Mediterranean peoples, and manifesting themselves as hemolytic anemia frequently associated with similar bone changes.

Summary and Conclusions. 1. A case of sickle-cell anemia in a white person is reported and the literature summarized. The case is associated with metastatic carcinoma.

2. Familial occurrence of the sickle-cell trait in offspring of the patient has been demonstrated.

3. An associated rheumatic endocardial lesion was present; this has been reported only once before.

4. The advanced age (54 years) for a first and fatal attack of hemolytic crisis is noted and the relationship to the coexisting malignancy discussed.

5. The relatively frequent occurrence of sickle-cell anemia among people of southern Italian and Mediterranean descent is again noted.

6. The need to consider the diagnosis of sickle-cell anemia in all cases of obscure hemolytic anemia is once more stressed.

REFERENCES

1. CLARKE, F.: Nebraska Med. J., **18**, 376, 1933.
2. COOKE, J. V., and MACK, J. K.: J. Pediat., 5, 601, 1934.
3. COOLEY, T. B., and LEE, P.: Am. J. Dis. Child., 38, 103, 1929.
4. GREENWALD, L., and BURRETT, J. B.: AM. J. MED. SCI., 199, 768, 1940.
5. HADEN, R. L., and EVANS, V. D.: Arch. Int. Med., 60, 133, 1937.
6. JOHNSON, F. B., and TOWNSEND, E. W.: South. Med. and Surg., 99, 377, 1937.
7. KLINEFELTER, H. F.: AM. J. MED. SCI., 203, 34, 1942.
8. MALLORY, T. B.: New England J. Med., 225, 626, 1941.
8a.MALLORY, T. B.: Personal Communication.
9. PERLMAN, L., and FOX, T. A.: Arch. Int. Med., 12, 177, 1941.
10. PONTONI, L.: Hematologica, 20, 657, 1939.
11. ROSENFELD, S., and PINCUS, J. B.: AM. J. MED. SCI., 184, 674, 1932.
12. SIGHTS, W. P., and SIMON, S. D.: J. Med., 12, 177, 1931.
13. VANCE, B. M., and FISHER, R. C.: Arch. Path., 32, 378, 1941.
14. WADE, L. J., and STEVENSON, L. D.: Am. J. Path., 17, 47, 1941.
15. WALKER, D. W., and MURPHY, J. P.: J. Pediat., 19, 28, 1941.
16. WAUGH, T. R.: AM. J. MED. SCI., 191, 160, 1936.
17. WEINER, S. B.: J. Mt. Sinai Hosp., 4, 88, 1937.
18. WHITBY and BRITTON: Disorders of the Blood, p. 251, 1935.

MAINTENANCE OF THE SEDIMENTATION RATE AS A TEST FOR MALIGNANT DISEASE

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IT is well known that the speed with which the erythrocytes in citrated or oxalated blood settle is retarded if the blood is allowed to stand for several hours before the test is set up. Koster[2] and Feldman[1] have reported the observation that this retardation is largely absent in the blood of patients with malignant tumors and Hodgkin's disease, so that the sedimentation rate after storage remains near the initial rate.

Koster[2] described 3 types of behavior in the blood from patients with cancer:

"Type I. The rate of sedimentation remains at the same level throughout the 24 hours, or at any rate the decrease does not amount to more than 20% of the initial value.

"Type II. The rate of sedimentation markedly increases above the initial value in the course of the estimations and does not decrease to below the initial value.

"Type III. After having risen to above the initial value the rate of sedimentation again decreases gradually, often to far below the initial value."

Koster reported that the blood of 95% of 112 patients with cancer and of 100% of 14 cases of Hodgkin's disease conformed to one of these 3 types. He did not indicate the frequency with which each type occurred, nor did he report results on a definite number of patients with non-malignant conditions.

Feldman did not mention Koster's Type III in his report, and stressed maintenance of the initial sedimentation rate as an indication of cancer. Though he did not state a crucial decrease in the rate at which a line between positive and negative results could be drawn, he stated that maintenance of the initial rate occurred in 95% of 118 cases of malignant disease, and retardation occurred in 94% of 55 cases of non-malignant disease.

If the work of Koster and of Feldman could be confirmed, an important easily performed test for cancer would be available. We have therefore determined the sedimentation rates of a number of patients in whom the presence or absence of malignant disease had definitely been established, immediately after the withdrawal of blood and after it had been stored, and have attempted to evaluate the comparative sedimentation rates as a test for malignant disease.

Method. In the beginning of our work we attempted only to evaluate the comparison of initial rates with the rates after 24-hour storage as a test for cancer. Readings were made 1 hour after the tests were set up, and the sedimentation rate expressed in millimeters per hour. Sterile sodium citrate (3.8%), in the proportion of 1 cc. to 4 cc. of blood, was used as the anticoagulant; the samples were stored in sterile rubber capped vials at room temperature, which in our laboratory was approximately 31° C. The method duplicates the one used by Feldman, with the exception that serial determinations after storage at various periods of time were not made.

The test was recorded as positive if after 24-hour storage there was a decrease of less than 20% of the initial sedimentation rate, and negative if the decrease was more than 20%. For the results of the test scatter diagrams were constructed plotting the initial rate against the rate after storage, and statistical methods applied to the data if inspection of the diagrams suggested the indication for such treatment. It was realized that by the method used bloods displaying behavior of Koster's Type III would be missed.

The first few tests revealed marked discrepancy between our results and those previously reported. Since temperature seemed to be the only variable in the method which could account for the discrepancy, successive variations were made in the temperature of the blood during its storage and during the determination of the sedimentation rate. Altogether tests were run under the following sets of circumstances: (1) Rate determination and storage at room temperature, approximately 31° C. (2) Rate determination at room temperature, storage at 10° C. (3) Rate determination and storage at 20° C. This duplicates the room temperature at which Koster's tests were made. (4) Rate determination and storage at 10° C.

Later serial determinations of the sedimentation rate over a 24-hour period were made, so as to observe the incidence of Koster's Type III behavior. For these determinations the blood was stored and the rates determined at 10° C., since only at this temperature, as judged by the other tests, did there seem to be any difference between the behavior of bloods from patients with and without cancer. The serial rates were plotted as curves.

Results. 1. *Rate Determination and Storage at 31° C.* This method was used for 8 cases of cancer and 16 cases of non-malignant disease. The test was negative in all 24 cases (Fig. 1). A glance at Figure 1

reveals the fact that there was almost complete retardation of sedimentation in all cases.

2. *Rate Determination at Room Temperature, Storage at 10° C.* This method was used for 11 cases of cancer and 20 cases of non-malignant disease. The test was positive in 9 of the cancer cases, negative in 1, and equivocal in 1. It was positive in 16 cases of non-malignant disease, negative in 3, and equivocal in 1 (Fig. 2). A glance at Figure 2 shows that the initial rate tends to be maintained in all cases except those with very low initial rates, and that there is no difference between the behavior of blood from patients with malignant tumors and from patients with other diseases.
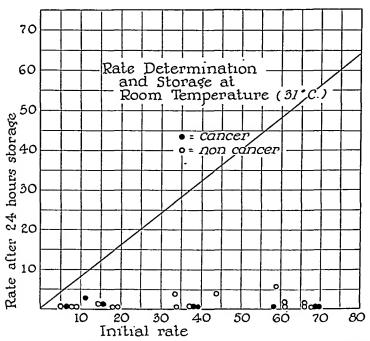
Fig. 1.—In this and in Figures 2, 3, and 4, "positive" tests lie above the diagonal line, and "negative" tests below it.

3. *Rate Determination and Storage at 20° C.* This method was used in 13 cases of cancer and 12 cases of non-malignant disease. The test was positive in 5 cases of cancer and negative in 8. It was positive in 3 cases of non-malignant disease, negative in 8, and equivocal in 1 (Fig. 3). In Figure 3 considerable scattering of the points is seen, indicating absence of the tendency for all tests to be negative, as in method 1, or positive, as in method 2, but there is no indication of difference in the behavior of bloods from patients with and without cancer.

4. *Rate Determination and Storage at 10° C.* This method was used for 31 cases of cancer and 39 cases of non-malignant disease. It was positive in 26 cases of cancer, negative in 3, and equivocal in 2. It
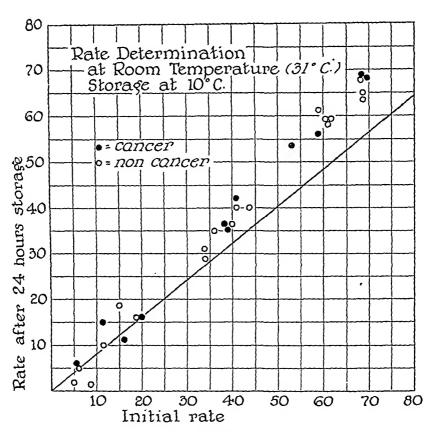
Fig. 2
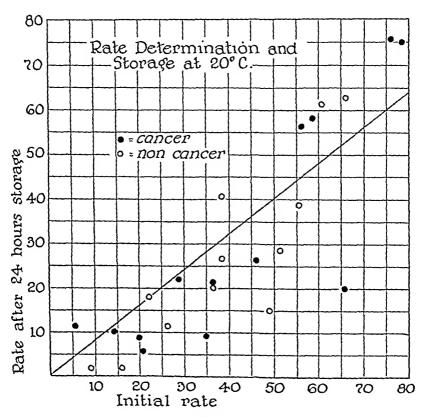
Fig. 3

was positive in 18 cases of non-malignant disease, negative in 17, and equivocal in 4 (Fig. 4). Statistical treatment of the data indicates that there is probably a significant difference between the mean percentile decrease in the sedimentation rates of the patients with and without cancer. As a test for cancer, the method gave approximately 85% correct, 10% false, and 5% doubtful results in the cancer cases; and 43% correct, 46% false, and 10% doubtful results in the non-cancer cases.
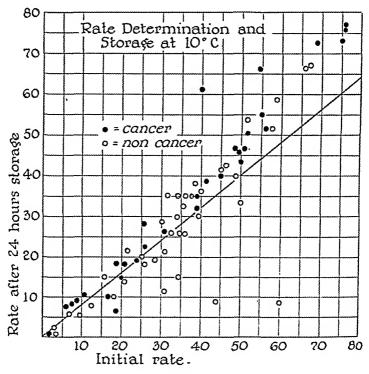
Fig. 4

5. *Serial Determinations, After 1, 2, 3, 4, 5, 6, and 24 Hours. Rate Determination and Storage at 10° C.* This method was used in 33 cases, 17 of cancer and 16 of non-malignant disease. In 5 of the cancer cases there was a definite increase in the sedimentation rate, amounting to 3 mm. or more at one time or another, and in 8 others there was a slight increase, amounting to less than 3 mm. (Fig. 5). However, in all of these 13 cases, the decrease in the rate after 24-hour storage was less than 20%, so that none fell into Koster's Type III. In 1 non-cancer case there was a definite increase, and in 8 a slight increase (Fig. 6). In all of these cases the decrease after 24-hour storage was less than 20%; they all therefore gave false positive reactions.

Discussion and Summary. Our results demonstrate that retardation or maintenance of the initial sedimentation rate in stored blood is capricious, and depends in large part upon the temperature of the
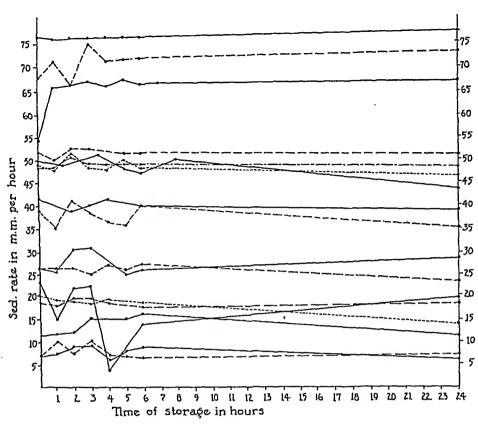
Fig. 5.—Serial sedimentation rates—cancer cases. In this and in Figure 6, solid and broken lines are used so that individual curves may be followed easily.
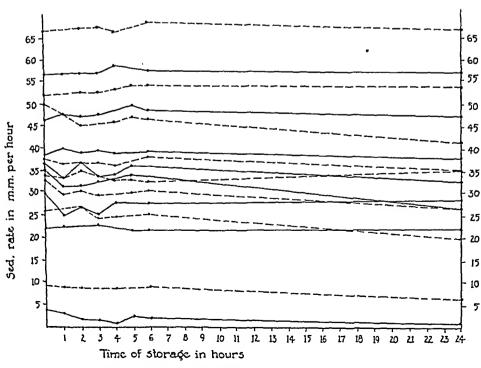
Fig. 6.—Serial sedimentation rates—non-cancer cases.

blood when the rates are determined and at which it is stored. We were able to find only one set of temperature circumstances at which there was significantly less retardation of the mean sedimentation rate in cases of cancer than in non-malignant diseases. When blood was stored 24 hours at 10° C. and the rates determined with the blood at the same temperature, the rate remained within 20% of the initial rate in about 4 cancer cases out of 5, and decreased more than 20% in a little less than half of the cases of non-malignant disease. One would therefore expect that in an unknown case a positive test would indicate that the chances of cancer being present are about 2 out of 3, while a negative test would indicate that there is only 1 chance in 5 that cancer is present. It is obvious that a negative test would give more information than a positive one, but that in either instance the test would be far from reliable. There is a strong probability, suggested principally by the high incidence of positive tests in persons without cancer, that maintenance of the initial rate is not related at all to the presence of cancer. The capriciousness of the test also suggests the possibility that the seemingly significant differences were due entirely to chance. This possibility is strengthened by the fact that the test is empirical, and cannot be correlated with any known differences between the blood cells or plasma of persons with and without cancer.

Conclusions. By the methods which we used, maintenance of the initial sedimentation rate in blood stored for 24 hours was not a reliable criterion for the presence of malignant disease.

REFERENCES

1. FELDMAN, H.: AM. J. MED. SCI., 200, 820, 1940.
2. KOSTER, L.: Acta med. Scand., 93, 420, 1937.

THE PROGNOSIS OF UNTREATED PATENT DUCTUS ARTERIOSUS AND THE RESULTS OF SURGICAL INTERVENTION

A CLINICAL SERIES OF 50 CASES AND AN ANALYSIS OF 139 OPERATIONS

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SINCE the first successful ligation of a patent ductus arteriosus by Gross and Hubbard in 1938,[4] we have been concerned with the problem of recommending surgery for such patients. During years of observation of a group of patients with patent ductus arteriosus, we were impressed with the apparent innocuousness of this lesion. Children observed through their entire school careers were able to carry on regular school activities with no restrictions and showed no evidence of cardiac disability at any time. Young men with this lesion have

worked at hard labor with no symptoms of cardiac strain. Women have borne children with no signs of heart failure. Such observations do not arouse enthusiasm for surgical intervention and we felt it necessary to carry on further studies before recommending such radical treatment. It seemed desirable to learn what could be expected in regard to longevity and cause of death in untreated cases of patent ductus arteriosus and to examine the record of surgery to date.

For these purposes three sets of data were assembled. Autopsy records on adults with patency of the ductus arteriosus were collected from the world literature and our own files; the analysis of these cases has been published elsewhere.[12] The clinical histories of our own patients, many of whom were observed for years, provide very useful data. Finally, the generous aid of surgeons and internists throughout the United States and Canada has provided us with clinical and surgical records on the majority of all the patients who have so far been operated upon to ligate the open ductus. The present paper is a report on our own experiences and on the surgical results to date.

Personal Observations. Recently we reported[13,15] the clinical findings on 23 patients with patent ductus arteriosus. Most of them had been observed over a period of years. At that time none of these patients had died and none had developed subacute bacterial endarteritis or serious cardiac failure. This was a young group, the average age being 20.3 years. With one exception they were well developed physically but most of them showed enlargement of the pulmonary artery and the hilar vessels. In only 4 instances was there evidence of progressive cardiac enlargement. Three of the latter patients were operated upon.

The first ligation in our series was attempted in a boy of 9 but the vessel ligated was probably not the ductus arteriosus. The physical signs were unchanged as a result of surgery and the boy's status was neither improved nor impaired. The second patient, a young man of 19, died as a result of rupture of the ductus at operation. The third operation, on a 10 year old girl, was a complete and impressive success.

Since the last report our series of patients has increased to 51, partly by new patients, partly by the follow-up of patients who had not been seen for some years. Thirty-seven of these patients have been thoroughly studied by physiologic methods devised in our laboratories.[8-11] Using criteria established elsewhere,[6,7] at least 20 of these patients might have been subjected to surgery. We chose, however, to delay surgical intervention until we could complete our studies and have only sent 3 additional cases to surgery. Three of these operations were apparently entirely successful; the fourth was Case 4 cited below.

The observations and experiences with these patients emphasize two features which point the opposing arguments about surgery. We shall illustrate by a few brief case notes:

Case Studies. CASE 1. A 58 year old male was admitted to the surgical service of Dr. O. H. Wangensteen with a diagnosis of carcinoma of the stomach. On physical examination evidence of patent ductus arteriosus was found and this was confirmed by careful physiologic studies. However, there was no
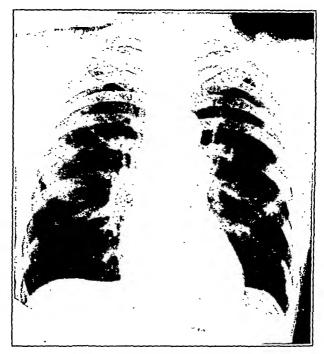
Fig. 1.—Teleroentgenogram of heart.
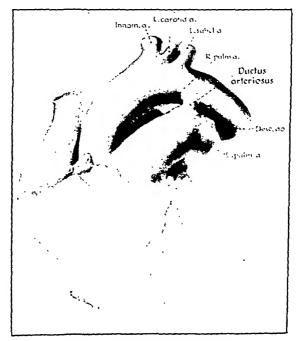
Fig. 2.—Drawing of the specimen.

indication of cardiac disability in spite of the fact that the patient had done hard manual labor all his life. He was subjected to total gastrectomy and withstood this severe surgical procedure without signs of a subnormal cardiac reserve. He eventually died of non-cardiac complications and postmortem revealed an enlarged heart and an open ductus arteriosus. Figure 1 shows teleroentgenogram of the heart and Figure 2 is a drawing of the specimen.
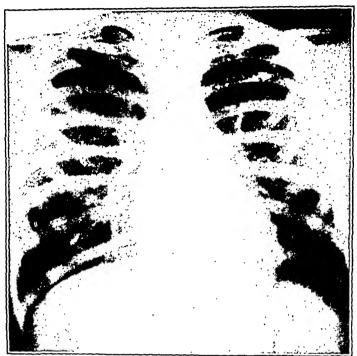
FIG. 3.—Case 2. Patent ductus arteriosus, with enlargement of the pulmonary artery age 10.
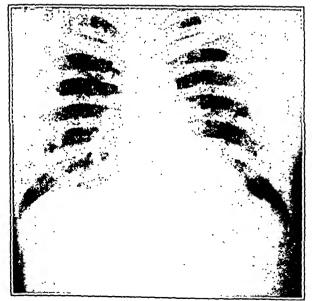
FIG. 4.—Same patient at age of 28. Still signs of enlargement.

CASE 2. A 28 year old male was examined after he had been rejected for military service because of "heart disease." We had examined him at the

age of 10 and had recorded then a diagnosis of patent ductus arteriosus with considerable enlargement of the pulmonary artery (Fig. 3). In the intervening 18 years he had felt himself to be perfectly well and was able to carry on very heavy manual work, including service in two C. C. C. camps. He had even passed an examination for life insurance. On reëxamination the evidence for patency of the ductus was undeniable. His heart was slightly enlarged and there were still signs of enlargement of the pulmonary artery (Fig. 4). He was free from symptoms and complaints and was unusually well developed and muscularly powerful.

CASE 3. A woman of 30 was first informed that her heart was not normal when she was examined incidentally to pregnancy. She exhibits all signs of typical patency of the ductus arteriosus. She has never had any symptoms or cardiac complaints. She went through labor without difficulty and in the 2 years since her baby was born she has done hard work with no cardiac embarrassment.

Obviously such observations do not indicate the necessity for surgery. Further argument for conservatism is suggested by the fact that 2 of our patients who have been followed for years have recently shown evidence of spontaneous closure of the ductus and disappearance of all signs of any lesion. The details of these 2 remarkable cases will be presented elsewhere. We believe that spontaneous late closure is very rare but it cannot be excluded as a remote possibility in the prognosis of any individual case.

On the other hand, our own recent experiences confirm the belief that a present status of good adjustment and freedom from cardiac disability in a patient with patency of the ductus arteriosus is no guarantee that subacute bacterial endarteritis may not intervene at any time or that cardiac failure may not eventually appear. Histories on 3 patients may be cited.

CASE 4. This 53 year old woman had always known that her heart was abnormal but had led a reasonably normal life without real cardiac disability until 6 months before death. Slowly progressive fever and weakness continued after a "cold" for several months before cardiologic consultation resulted in the diagnosis of patent ductus arteriosus and subacute bacterial endarteritis. By the time consent for surgery was obtained the woman was practically moribund and she died an anesthetic death on the operating table before surgery was started. Postmortem examination fully confirmed the diagnosis and revealed a patent ductus that would have provided a minimum of operative difficulty for ligation had this been attempted before her final illness.

CASE 5. The diagnosis of patent ductus arteriosus was made in this 16 year old girl when she was 7 years of age. She was subsequently carefully studied and w: - ·· ···!·-! ·· ·· -·---- candidate for ligation but her general freedom from (··· · · ··· · · · ·· made it appear that there was no immediate necessity to insist on surgery in the face of parental unwillingness. A month before death she had apparently been in her normal health when she suddenly complained of dizziness, chills, and fever. She died in 4 weeks of subacute bacterial endarteritis with pulmonary infarcts, vegetations in the pulmonary artery and valve and a heavy infection of *Streptococcus viridans*. We were only apprised of these developments by the family physician after the patient expired. Our original diagnosis was confirmed at autopsy.

CASE 6. This 46 year old woman came in for consultation from her office work with complaints of recently developed dyspnea and palpitation. She had been told early in life that she had a cardiac disorder but this had never seriously inconvenienced her before. At examination she was in well-marked

failure but no murmurs could be heard.   She died in failure within 2 weeks. At autopsy the heart was found to be enlarged and there was a large patent ductus arteriosus with no other defects.

Reports in the Literature.   A study of the recent literature failed to give us data which could be used to predict what could be expected in patients with patent ductus arteriosus who receive no treatment. We found it necessary, therefore, to review the entire medical literature and we have analyzed all the cases of patent ductus arteriosus in adults from which postmortem examinations have been reported.   The details of this study are given elsewhere.

Briefly, it may be stated that 80% of such patients eventually succumb to their cardiac lesion.   These patients who were alive at 17 years of age averaged 35 years of age at death.   At least 40% of these patients died of subacute bacterial endarteritis and most of the remainder died of congestive cardiac failure.   Spontaneous rupture of the pulmonary artery or the ductus occurred in a few cases.

The age distribution of our own patients likewise indicates that the life expectancy of persons with untreated patency of the ductus arteriosus is considerably shortened.   It is true that the majority of our patients were found in a children's clinic but we have made considerable efforts to find adult cases with no great success.   The average age of the entire series of 51 patients is less than 25 years and the oldest patient in the series died at 58.   These data from the literature and our own series force a reconsideration of a conservative attitude toward what might seem radical surgery.

The Surgical Record.   From the current literature, but mostly through personal correspondence with individual surgeons and internists, we have obtained and analyzed the data on nearly all patients on whom ligation of the ductus has been attempted.   The record is surely not complete but we are certain that it contains the great majority of operations done at the time of writing.

One hundred and forty patients have been operated upon by a total of 25 surgical teams.   Of these cases, 107 were uncomplicated, while operation was performed on 33 patients in the presence of subacute bacterial endarteritis.   Seven of the patients were in our own series.

In the 107 uninfected cases, 81 operations were completely successful, that is, the murmur and thrill disappeared and the pulse pressure decreased.   In a number of these successful cases, a distant short systolic murmur remained over the pulmonic area.   It is our impression that this murmur results from the persistent dilatation of the pulmonary artery and not from persistent patency of the duct.   In 14 instances, however, the continuous machinery murmur was not permanently obliterated after surgery.   The murmur returned in from a few weeks to several months after operation.   It is quite probable that in these 14 instances, there was a recanalization of the duct due to failure of the ligature material to hold.   It is obvious that further research must be carried on in order to find the perfect ligature material and method of ligation.

In 6 cases, death resulted from rupture of the duct at operation.

From recent studies, it is quite certain that this accident will not occur as frequently in the future. Surgeons have already perfected their methods to avoid this complication. In 2 instances, subacute bacterial endarteritis developed after operation. This is rather disturbing but it is reasonable to assume that the rest of the patients who have been operated upon and who have been followed over a period of months or years will probably not develop infection as result of the surgery. In 1 case, death resulted from infection of the surgical wound followed by mediastinitis. In another case, that of a physician 39 years of age, a direct arteriovenous communication was found between the pulmonary artery and the aorta. Fortunately, the surgeon had the good judgment to terminate the operation without attempting ligation. The patient is none the worse for his experience. A study of patent ductus arteriosus in the adult reveals reports of a number of instances of arteriovenous fistulæ too short to ligate. At present it is impossible to diagnose such a direct communication and there will be other instances when surgeons will meet with this inoperable situation.

A vessel other than the ductus was ligated in 3 cases. In 1 instance the aorta was mistaken for the duct and, of course, ligation resulted in death. In another instance, a strand of fibrous tissue was mistaken for the duct and this patient also died as the result of the operation. The third case resulted in no harm to the patient.

It is a remarkable fact that errors in diagnosis were made in only 2 instances in the entire group of 140 patients. It is, therefore, apparent that the diagnosis of patent ductus arteriosus can be made with security. The old idea that it was hazardous to tie off the duct because the patent ductus might be acting as a safety shunt for other congenital cardiac lesions need no longer be seriously considered. In those instances where the ductus does act as a safety shunt there are always complicating congenital developmental defects which should not be difficult to differentiate from the simple uncomplicated patent ductus arteriosus. Nine deaths have resulted from these 107 operative cases; a mortality rate of 8.5%.

Of the 33 patients who were operated upon in the presence of subacute bacterial endarteritis, 20 resulted in apparent complete success; that is, the blood cultures became sterile and the patient's general condition improved markedly. Some of these patients have been followed only a period of months, not long enough to draw definite conclusions, but some have certainly been restored to completely normal health. Five patients died on the operating table as the result of hemorrhage. In 8 instances, the fever persisted in spite of the ligation of the duct. Somewhat more than 50% apparent success in a group of cases in which previously 100% mortality was to be expected can be considered an excellent result.

Discussion. The data in this paper were assembled in the hope that practical conclusions would emerge from their analysis. We believe that certain conclusions are, in fact, clearly indicated and that some recommendations can now be made with confidence. Surgery is advisable in the great majority of patients with patent ductus arteriosus with or without subacute bacterial endarteritis. In the latter case

surgery affords more than a forlorn hope. The uninfected patient cannot expect a normal life span without surgery and is liable to develop subacute bacterial endarteritis at any time in spite of present apparent well-being.

The experience of Touroff and other surgeons operating in the presence of subacute infection shows that ligation should be attempted immediately when the diagnosis is made. The continued presence of the infection renders the operation much more hazardous because of increasing edema and friability of the ductus and adjacent tissues. Moreover establishment of vegetations on the heart valves creates pockets of infection which may persist after the abnormal shunt of blood is stopped. In a number of cases ligation in these patients brought about temporary amelioration but persistent bacterial endocarditis had already been established and the patients eventually succumbed. It seems certain that sulfa drugs, fever therapy and transfusions have only a delaying action at best. Trial of a course of such treatment before surgery is only to increase the risk of delay.

Successful ligation of the uninfected duct will prevent congestive heart failure. However, it cannot be stated with certainty that the danger of subacute bacterial endarteritis is entirely removed by ligation. It is reasonable to hope at least that the liability to infection will not be increased by surgery. Definite conclusions must wait until these operated patients have been observed for years. In 2 cases subacute bacterial endarteritis developed after surgery. In 1 of these the duct had recanalized. Even without recanalization it must be admitted that the blind pouches in the aorta and pulmonary artery represent favorable sites for the development of infection in the same way that any cul-de-sac in an area of exceptionally turbulent blood flow is a potential spot for infection. However, we can believe that the remaining pouches are less dangerous than the open ductus in this regard. For one thing, the persistently open ductus almost always leads to the development of atheromata and roughening of the wall of the pulmonary artery and thus creates a specially vulnerable region. Finally, if turbulence *per se* is favorable to infection then the ligated ductus is much safer; the extent of turbulence can be gauged roughly by the intensity of the murmur.

The incidence of subacute bacterial endarteritis is small until the patients are in their teens and the highest incidence is in the third decade of life. It might be suggested therefore that there is slight danger in delaying surgery in very young children. This is not entirely true. The incidence of infection in young children is not entirely negligible and the difficulty of the surgery itself is increased with increasing age. Progressive enlargement of the pulmonary artery and possible relative shortening of the ductus tend to obscure and to reduce the safe field of operation. The rapidity of recovery of young children from the operation is astonishing.

The diagnosis of patent ductus arteriosus can be made with great assurance. We have noted that in the entire series of 140 operations, only 2 diagnostic errors were made. In both of these the data collected by the internists were incompatible with the diagnosis.

Very rarely there may be a direct open communication between the ascending aorta and the pulmonary artery. Fraentzel,[2] Oberwinter,[14] and Girard[3] have reported such cases. These would be indistinguishable from a true patent ductus but would, of course, be inoperable. More frequently, but still only rarely, the ductus may be so short as to be inoperable; it may even be reduced to a hole between aorta and pulmonary artery at the normal ductus site. We must depend on the ability of the surgeon to recognize such a condition in the surgery and to retreat without pursuing a dangerous dissection.

TABLE 1.—SUMMARY OF THE RESULTS OF SURGICAL INTERVENTION IN PATIENTS WITH PATENT DUCTUS ARTERIOSUS

Total number surgeons	25
Total number cases operated	140
Number uninfected cases	107
1. Completely successful	81
2. Continuous murmur persists	14
3. Rupture of duct at operation	6
4. Operation followed by subacute bacterial endarteritis	2
5. Infection of wound and mediastinitis	1
6. Found inoperable	1
7. Vessel ligated not ductus arteriosus	3
8. Error in diagnosis	2
9. Total number dead after operation	9
Cases operated upon with subacute bacterial endarteritis	33
1. Completely successful	20
2. Died at operation	5
3. Fever persists after successful ligation	8

The low mortality rate indicated in Table 1 is gratifying and surprising in view of the serious nature of the operation. It is a tribute both to the skill of the individual surgeons and to the development of thoracic surgery in recent years. It is necessary to emphasize, however, that both skill and extensive experience in thoracic surgery are required to undertake the operation. This is exemplified by the fact that two surgeons, Dr. Robert Gross,[5] of Boston, and Dr. John C. Jones,[7] of Los Angeles, have done more than half of all the ligations to date with mortality rates less than half that for the other surgeons who have devoted less attention to this particular operation. In general, we can expect that accurate diagnosis and skilled surgeons can guarantee us a mortality of about 5% in uninfected cases.

Summary and Conclusions. 1. Diagnosis of patent ductus arteriosus can be made with great certainty, and complications making surgical ligation inadvisable are readily recognized.

2. The great majority of patients with this defect suffer no serious disability or restriction of activity during most of their lives, but their life expectation is greatly shortened by the continued presence of the defect.

3. Experience to date shows that ligation of the uninfected ductus can be made with a mortality of less than 10%.

4. Ligation of the ductus in the presence of subacute bacterial endarteritis offers an even chance of survival in the face of practically certain death without ligation.

5. The danger of development of subacute bacterial endarteritis after successful ligation cannot properly be estimated as yet.

6. Six case histories are cited which illustrate opposing arguments for and against ligation.

7. An analysis is presented of the results of 140 operations to ligate the ductus.

8. It is concluded that the majority of patients with patency of the ductus arteriosus should be sent to surgery for ligation after careful clinical studies have been made on them.

9. Ligation should be attempted immediately if subacute bacterial endarteritis develops.

10. Ten patients with uninfected patent ductus arteriosus have been operated upon by Dr. O. N. Wangensteen at the University of Minnesota Hospital, the last 8 cases with complete success. As far as is known, in none of them has there been a recurrence of signs indicating recanalization.

REFERENCES

1. BOURNE, G., KEELE, K. D., and TUBBS, C. S.: Lancet, 2, 444, 1941.
2. FRAENTZEL, O.: Virchow's Arch., 43, 420, 1866.
3. GIRARD, E.: Über einen Fall von kongenitaler Kommunikation zwischen Aorta und Arteria pulmonalis, Inaug.-Diss., Zürich, 1895.
4. GROSS, R. E., and HUBBARD, J. P.: J. Am. Med. Assn., 112, 729, 1939.
5. GROSS, R. E.: Surgical Closure of the Patent Ductus Arteriosus, Modern Concepts Cardiovasc. Dis., 10, No. 12, 1941.
6. HUBBARD, J. P., EMERSON, P. V., and GREEN, N.: New England J. Med., 221, 481, 1939.
7. JONES, J. C., DOLLEY, F. S., and BULLOCK, L. T.: J. Thor. Surg., 9, 413, 1940.
8. KEYS, A.: Am. J. Physiol., 134, 268, 1941.
9. KEYS, A., and FRIEDELL, H. L.: Am. J. Physiol., 126, 741, 1939.
10. KEYS, A., and FRIEDELL, H. L.: Proc. Soc. Exp. Biol. and Med., 401, 556, 1939.
11. KEYS, A., FRIEDELL, H. L., GARLAND, L. H., MADRAZO, M. F., and RIGLER, L. H.: Am. J. Roentgenol., 44, 804, 1940.
12. KEYS, A., and SHAPIRO, M. J.: Am. Heart J., 25, 158, 1943.
13. KEYS, A., VIOLANTE, A., and SHAPIRO, M. J.: Arch. Latino Am. cardiol. hematol., 10, 237, 1940.
14. OBERWINTER: München. med. Wchnschr., 51, 1610, 1904.
15. SHAPIRO, M. J., and KEYS, A.: New Internat. Clin., 4, 148, 1941.
16. TOUROFF, A. S. W., VESELL, H., and CHASNOFF, J.: J. Am. Med. Assn., 118, 890, 1942.

CLINICAL SIGNIFICANCE OF HYPERVENTILATION

THE RÔLE OF HYPERVENTILATION IN THE PRODUCTION, DIAGNOSIS AND TREATMENT OF CERTAIN ANXIETY SYMPTOMS

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PATIENTS with anxiety frequently come to the physician complaining of dyspnea, giddiness, fainting and coldness of the extremities. The physician usually recognizes that no organic disease is present, but he is unable to explain to the patient the manner in which anxiety has

produced the symptoms. In recent years the physiologists have called attention to various mechanisms by which afferent stimuli arising from the emotional content of thought or from various sensory nerves can produce changes in function. The clinician has gradually realized that reflex disturbance in function is the physiologic basis of many of the symptoms of which his psychoneurotic patients complain. It is well known that sensory stimuli can cause abdominal pain by reflex contraction of the stomach or colon. Studies on the carotid sinus reflex have demonstrated that sensory stimuli can cause symptoms by cardiac standstill or marked lowering of the arterial pressure. The purpose of this paper is to point out how afferent stimuli arising from the emotional content of thought or from sensory nerves may affect the respiration and thereby produce clinical symptoms.

Normal respiration is controlled by both nervous and chemical factors. Although in the past many textbooks have stressed the importance of the chemical factors, it is now recognized that many of the variations in breathing occurring in everyday life are due to reflex stimuli.[2] The afferent impulses arise from moving muscles, various viscera, eyes and ears, any sensory nerve ending, and particularly from the emotional content of thought. The lay public has long realized that emotions influence the respiration. The breath is held during a moment of suspense, and the respiratory rate is increased with sexual excitement. Finesinger[4] has studied the effects of pleasant and unpleasant thoughts on the respiration and has demonstrated this type of respiratory control in the laboratory.

When an individual's respiration is increased by sensory or emotional stimuli, he may complain either of dyspnea or of certain other symptoms, such as giddiness, light-headedness or fainting, which are secondary to the disturbance in cerebral metabolism brought on by the overbreathing. When the respiration is increased by a reflex mechanism without a corresponding rise in cerebral metabolism, the carbon dioxide content of the alveolar air is diminished and, because of the rapid diffusibility of that gas, a rapid loss of carbon dioxide from the body occurs. This results in alkalosis, and associated with this there is an alteration in cerebral metabolism caused either by the increased alkalinity of the arterial blood or indirectly by decreased cerebral blood flow. The disturbance in cerebral metabolism is shown by the development of cerebral symptoms and by the appearance of bizarre waves in the electroencephalogram.[3] The rise in pulmonary ventilation secondary to exercise does not produce alkalosis because the increased loss of carbon dioxide through the lungs is balanced by the increased production of carbon dioxide and organic acids as a result of the increased metabolism.

The ease with which cerebral symptoms are precipitated by voluntary hyperventilation and the order in which they occur are subject to considerable variation.[2,5,6,9,11,12] They have been described as a feeling of light-headedness, unsteadiness, faintness, or a far-away feeling. This sensation is followed by numbness and tingling of the tongue, mouth and extremities. The hands become cold and pale

and a tremor may appear. If the subject is standing, syncope may occur. Tetany occurs as a late symptom with tightness of the muscles, increased reflex irritability, and finally carpopedal spasm. The Chvostek sign may become positive. The mental reactions of the subjects vary tremendously; some have almost no change, others may become excited, weep and complain bitterly of the symptoms produced, and may have difficulty in stopping the procedure. On rare occasions rebreathing into a paper bag may be necessary to stop the hyperventilation.

When a normal subject hyperventilates voluntarily, he recognizes the cause of his symptoms and is not alarmed; but the patient who hyperventilates unknowingly develops the symptoms without apparent cause and he, as well as his physician, may fear that they indicate the presence of serious organic disease. The symptoms of which the patient complains may be attributed to overbreathing if they are produced by forced respiration and if they disappear on holding the breath. The initial symptoms appear with equal ease in the normal subject and in the patient. The significant fact is that the symptoms which bring the patient to the physician can be faithfully reproduced in the patient by the forced breathing.

In the last 3 years it has been our custom to determine the effects of hyperventilation in patients who (1) complain of light-headedness, giddiness, far-away feeling, feeling of unreality, numbness of face, mouth and hands, carpopedal spasm, and fainting; (2) complain of dyspnea in the absence of demonstrable signs of congestive failure. The patients studied complained of the same symptoms which occurred in normal control subjects during forced breathing.

To test the response to hyperventilation the patient is instructed to breathe deeply and rapidly. Frequently it is advisable for the physician to demonstrate what is desired, and during the test the patient must be encouraged repeatedly to continue breathing vigorously and not relax his efforts. If the problem is one of fainting, the test should be carried out in the upright position, for it is only rarely that loss of consciousness develops in the recumbent position. In the majority of instances a 2 or 3 minute period of vigorous hyperventilation is sufficient. The physician observes the objective effects while the patient is breathing deeply, and when he feels that there has been adequate hyperventilation he questions the patient about his symptoms.

Cerebral Effects of Hyperventilation. The history of patients who faint from hyperventilation is fairly characteristic. They frequently feel light-headed and giddy when lying down and notice numbness of the face and extremities. They think they are going to lose consciousness but rarely do so. The occurrence of symptoms when the patient is in the recumbent position rules out postural hypotension as the cause of the fainting. When sitting and standing they have many of these abortive attacks which, from time to time, are followed by the loss of consciousness. Syncope results from the combination of the decrease in cerebral blood flow produced by pooling of blood in the lower extremi-

ties and the disturbance in cerebral metabolism caused by the alkalosis. In the last 3 years 20 patients with this syndrome have been observed by us. The following case history is illustrative of this group.

Case Studies. CASE 1. An 18-year old student nurse was admitted to Grady Hospital because of repeated attacks of syncope. In the past she had fainted occasionally, but never often enough to cause her any concern. Recently, however, syncope had occurred so frequently that she was afraid of being dismissed from training school. The loss of consciousness occurred only when she was sitting or standing, never when she was lying down. Before losing consciousness the patient felt light-headed and, as she described it, had a far-away feeling. Her hands and feet were cold, and there was a tingling sensation about her mouth, down the arms, and down the inner surfaces of her thighs. Frequently the prodromal symptoms were not followed by syncope. They occurred regardless of whether the patient was standing or lying down, although syncope did not occur when the patient was recumbent. Consciousness returned quickly after the patient fell to the floor. Recovery was complete within a few minutes, and the patient would return to work immediately thereafter. There was no history of biting the tongue or of incontinence of urine or feces. The patient had always been healthy. She performed her work with ease and participated in sports without difficulty. The routine physical examination and laboratory findings were normal.

Pressure on either carotid sinus did not cause faintness or marked change in pulse rate, indicating that carotid sinus irritability was not responsible for her fainting. On standing motionless for several minutes the pulse rate increased normally and there was only a slight narrowing of the pulse pressure, ruling out the possibility of postural hypotension. The patient was then instructed to sit upright in a chair and breathe as deeply as possible. After a few breaths she complained of giddiness, blurred vision, numbness and tingling of the arms and legs, and then became unconscious. The heart rate was rapid but the pulse pressure remained unchanged. The hands and feet were cold. The patient was placed in the horizontal position and after a few seconds of apnea, consciousness was recovered. The patient stated that this fainting attack was exactly like the ones which she had suffered previously. Hyperventilation was then carried out in the recumbent position. Giddiness, feeling of unreality, numbness and tingling of the face, arms and legs and coldness of the hands and feet resulted, but the patient did not lose consciousness.

Case Comment. This patient was an anxious young woman who responded to a variety of stimuli with a reflex increase in respiratory rate. The overbreathing caused alkalosis and produced a giddy, uncertain feeling. This sensation frightened her and caused further increase in pulmonary ventilation with the accentuation of the cerebral symptoms. Numbness and tingling developed around the face and in the extremities, causing still greater anxiety. If the patient was recumbent, the disturbance in cerebral metabolism caused by the alkalosis did not become severe enough to cause loss of consciousness. The fainting episodes embarrassed the patient. Every time that she felt slightly giddy, she immediately became afraid that she would faint. This caused more overbreathing and at times syncope.

The mechanism of the attacks of syncope was explained to the patient. She was told that because of her own biologic makeup and personality structure a variety of stimuli would continue to cause a reflex increase in pulmonary ventilation and that when this occurred she would experience the sensations of giddiness and light-headedness. She was told that these sensations were a normal response to over-

breathing, were physiologic rather than pathologic, and would disappear if she held her breath. The patient has had no further difficulty. She interprets correctly the cerebral symptoms of overbreathing so that they no longer cause anxiety and the vicious cycle has been broken.

Though the emotional control of thought is the most common stimulus for overbreathing, sensory impulses from any part of the body may be responsible for the hyperventilation. In the following case history afferent stimuli from the bladder produced the overbreathing.

CASE 2. An elderly colored man with a moderate degree of hypertension, but no signs of cardiac decompensation, was admitted to the Peter Bent Brigham Hospital because of a chronic urethral stricture and an irritable, infected bladder. Bladder drainage was accomplished by an inlying urethral catheter. Later in the day the patient began to breathe deeply, and shortly afterward became unconscious. At first it was thought that he had developed cardiac asthma, but examination failed to reveal evidence of cardiac decompensation. Then it was noted that the tube leading from the catheter was twisted, causing the flow of urine to become obstructed. As soon as the bladder was emptied, the respiration became much quieter and the patient regained consciousness. Similar episodes occurred several times during his hospitalization.

Case Comment. These 2 patients are similar in that their symptoms were the result of hyperventilation. They demonstrate that the increased respiratory rate may be due to a variety of causes, and the presenting symptoms may be any of the symptoms of overbreathing.

Hyperventilation With Dyspnea. Certain patients with an adequate circulation come to the physician complaining primarily of dyspnea. This may be present at rest, on slight exertion or on awakening at night. A carefully taken history frequently reveals that the dyspnea is accompanied by other manifestations of hyperventilation such as dizziness, giddiness, light-headedness, numbness of hands and feet, coldness of the extremities and drawing of the hands. During the last 3 years we have observed 15 patients in whom the dyspnea of anxiety was mistaken for the dyspnea of congestive failure. These patients had no evidence of circulatory insufficiency and their symptoms could be reproduced by a short period of hyperventilation. Some of these patients had no signs of any organic disease; others had hypertension or rheumatic heart disease with no evidence of cardiac decompensation. The following case history is typical of this group.

CASE 3.—A 44-year old housewife complained of dyspnea on exertion and of paroxysmal nocturnal dyspnea of 4 years duration. She had been told that she had an elevated blood pressure and albuminuria. On many occasions the attacks of nocturnal dyspnea had been severe enough to require the administration of morphine. The patient had a difficult home situation and had been to a number of doctors in the last few years because of headache and neurodermatitis. The arterial pressure was 160/110 mm. Hg. Otherwise the physical examination was negative. The urine contained 2+ albumin. The phenolsulfonphthalein excretion was within normal limits. Roentgenographic examination showed that the heart was at the upper limits of normal in size with a prominent left ventricle. The lungs were clear, and there was no edema. The vital capacity was normal.

The patient was given digitalis and told to return in 1 week. She knew that digitalis was prescribed for heart disease and that she had convinced her doctor

that she had heart disease.   During the next day the patient became progressively more dyspneic.   Late that afternoon she was admitted to the Peter Bent Brigham Hospital.   The patient was breathing deeply and rapidly, the hands were cold and there was bilateral carpopedal spasm.   She complained of numbness of the face and extremities.   After rebreathing into a paper bag for a few minutes, the patient became quiet and the dyspnea disappeared. Further questioning revealed that the patient had had repeated attacks of dizziness and light-headedness during the preceding 4 years.   The attacks of nocturnal dyspnea were all accompanied by cold hands and feet, light-headed-. ness and numbness of the face and extremities.   It now seemed clear that she had never had any symptoms of heart failure, but that all her symptoms could be attributed to reflex hyperventilation.

The mechanism by which anxiety caused an increase in respiratory rate was explained to the patient.   She accepted the fact that she did not have heart disease, but later her anxiety expressed itself as globus hystericus and pain in the abdomen.

Comment.   These experiences stimulated our interest in patients with apparently compensated heart disease who complained of dyspnea.   Patients with mitral stenosis without any objective sign of congestive failure were examined.   These subjects had normal vital capacities, but had complained of dyspnea for years.   In some of these subjects voluntary hyperventilation produced a typical anxiety panic. They interpreted the feeling of light-headedness and numbness in the face and extremities as symptoms of heart disease.   Questioning revealed that the dyspnea of which they had complained was accompanied by cold hands and feet, light-headedness, and numbness and tingling.   Exercise tests showed that these patients were no more dyspneic on exertion than normal subjects.

It gradually became clear that the diagnosis of cardiac disease evoked some anxiety in every patient.   If this anxiety caused overbreathing, the patient invariably interpreted the resulting symptoms as an indication of cardiac failure.   It is helpful if the patient realizes that many things other than heart failure or cerebral disease can cause the sensations of unreality, giddiness, and dyspnea.   This is accomplished by having every patient with compensated heart disease overbreathe during the course of the physical examination.   The patient is then questioned about his symptoms and his interpretation of them.   The underlying physiologic mechanism producing the symptoms is then explained.

At least two different mechanisms appear to be operative in the dyspnea of anxiety.   In the first type described here there is a marked increase in pulmonary ventilation.   This increase in respiratory rate may result solely from emotional stimuli, or it may be an exaggerated response to some somatic stimulus, such as walking slowly, which would normally cause only a slight increase in pulmonary ventilation. In the second type, not discussed in this paper, the patient is conscious of the effort in breathing at rest.   He may complain of breathlessness even when there is little actual change in pulmonary ventilation.

Hyperventilation is of importance in other conditions.   In many patients with epilepsy, petit mal attacks can be precipitated by over-

breathing.[7] Grand mal attacks are not produced in this manner. Various authors have pointed out that many of the symptoms of neuro-circulatory asthenia are caused by hyperventilation.[1,8,14] Probably the hyperventilation is a sign of the underlying psychoneurosis and therefore it is the result rather than the cause. Recent studies have suggested the importance of hyperventilation in aviation medicine.[10,12]

The average physician pays little attention to the physiologic mechanisms underlying the complaints of his psychoneurotic patients. The symptoms are real to the patient, but they frequently remain vague and indefinite to the doctor. Clinical observation and study of the physiologic changes underlying these symptoms will be of benefit to both patient and physician.

Summary and Conclusions. 1. Respiration is controlled by both, reflex and chemical mechanisms. The variations in respiration which occur during our daily routine of living are caused chiefly by reflex phenomena. Afferent stimuli from any organ in the body or from the emotional content of thought may cause the pulmonary ventilation to be increased beyond the level required by the metabolism of the body. This reflex increase in respiration furnishes the physiologic basis for many of the symptoms of the psychoneurotic patient. The patient may be conscious of the hyperventilation itself and complain primarily of dyspnea, or he may complain of any of the resultant symptoms, not being aware of the increased pulmonary ventilation.

2. Voluntary hyperventilation in normal subjects produces a disturbance in cerebral metabolism with variable symptoms. Usually faintness, giddiness or some similar complaint.is followed by numbness and tingling about the mouth and extremities; the hands become cold, and if the patient is standing he may faint. Prolonged hyperventilation may produce signs and symptoms of tetany.

3. Any of the cerebral symptoms produced by voluntary hyperventilation may appear in the anxious patient who unknowingly hyperventilates. Production of these symptoms by voluntary overbreathing is not only of diagnostic aid, but is useful in demonstrating to the patient that his symptoms have a physiologic rather than a pathologic basis.

4. At times the hyperventilation itself may be noted by the patient and may appear as a symptom, particularly in patients with cardiac disease without congestive failure or in patients who fear cardiac disease. Associated with this breathlessness there may be other symptoms of hyperventilation.

5. Observation of the effects of voluntary hyperventilation should be a routine procedure in the examination of: (1) patients complaining of fainting, giddiness, or a far-away feeling; and (2) patients with breathlessness, particularly those with cardiac disease without evidence of congestive failure.

REFERENCES

1. Annotations, Lancet, 1, 322, 1940.
2. BEST, C. H., and TAYLOR, N. B.: The Physiological Basis of Medical Practice, 2d ed., Baltimore, Williams & Wilkins Company, 1940.

3. Davis, H., and Wallace, W. McL.: Arch. Neurol. and Psychiat., 47, 606, 1942.
4. Finesinger, J. E.: Arch. Neurol. and Psychiat., 42, 425, 1939.
5. Fowweather, F. S., Davidson, C. L., and Ellis, L.: Brit. Med. J., 2, 373, 1940.
6. Fraser, R., and Sargent, W.: Brit. Med. J., 1, 378, 1938.
7. Gibbs, E. L., Lennox, W. G., and Gibbs, F. A.: Arch. Neurol. and Psychiat., 43, 223, 1940.
8. Guttmann, E., and Jones, M.: Brit. Med. J., 2, 736, 1940.
9. Harwood, R.: New England J. Med., 218, 602, 1938.
10. Hinshaw, H. C., and Boothby, W. M.: Proc. Staff Meet. Mayo Clin., 16, 211, 1941.
11. Kerr, W. J., Dalton, J. W., and Gliebe, P. A.: Ann. Int. Med., 11, 961, 1937.
12. Rushmer, R. F., Boothby, W. M., and Hinshaw, H. C.: Proc. Staff Meet. Mayo Clin., 16, 801, 1941.
13. Sargant, W.: Lancet, 1, 314, 1940.
14. Soley, M. H., and Shock, N. W.: Am. J. Med. Sci., 196, 840, 1938.

A MODIFIED CHRISTIE METHOD FOR RESIDUAL AIR MEASUREMENTS

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CENTRO DE INVESTIGACIONES TISIOLÓGICAS, BUENOS AIRES, ARGENTINA

A METHOD for the measurements of the functional residual air, based on the dilution of the nitrogen in the lung was described by Christie[4] in 1932 (review of literature). A spirometer filled with oxygen was attached to the test subject. The carbon dioxide was removed with soda lime, and the subject rebreathed in the circuit until nitrogen equilibrium was reached throughout the lung-spirometer system. The functional residual air was calculated from the composition of the gas in the spirometer. It was assumed that after 5 or 7 minutes of quiet breathing, gas equilibrium was complete in lungs and spirometer, except for a slightly greater concentration of nitrogen in the lungs. This excess was assumed to be the same as that occurring during the breathing of room air. A correction for the nitrogen excretion in the lungs was made.

Lassen, Cournand and Richards[13] found a lower concentration of nitrogen in the lungs than in the spirometer at the end of the rebreathing period. They called this effect "oxygen storage" and attributed it to the decreasing volume of gas in the spirometer due to oxygen consumption. They corrected the oxygen storage effect by introducing the alveolar nitrogen concentration in the calculation of the residual air.

Herrald and McMichael[10] proposed to keep the spirometer volume constant with a continuous oxygen flow during the rebreathing period, in order to avoid the oxygen storage effect.

Anthony,[1] using the hydrogen dilution method, found no storage effect, provided that the spirometer volume was at least 3 times larger than the expected residual air. It should be noted that he used a spirometer equipped with a powerful blower.

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Keltreider et al.[11] found that the alveolar percentage of nitrogen was higher than in the spirometer.   However, the difference was less than than between alveolar nitrogen, before the rebreathing period, and atmospheric air.

Cournand et al.[5] presented the results of functional residual air measurements using the original Christie method, the Lassen et al. modification, the constant volume technique of Herrald and McMichael and the increasing lung nitrogen method.   The results gave agreement by all methods in 4 normal subjects only, 3 of whom had small residual air volume.   In the 2 other normal subjects there were wide discrepancies between the results with different methods.   Keeping the spirometer volume constant did not correct the discrepancies. They consider the data presented as a positive evidence of unequal gas distribution within the lungs.

Darling et al.[8] and Cournand et al.[6] used a new open circuit method to avoid the inadequacy of the closed circuit method.   The reasons of such inadequacy would be: (1) the changing composition of inspiratory gas mixture, due to reduction of the spirometer gas volume as oxygen is absorbed; (2) difficulties in the exact calculation of the oxygen absorbed in some subjects; (3) magnification of any error in the final residual air value due to the small net change in lung nitrogen concentration, usually no more than 0.3 of an atmosphere.

In the open circuit method the subject is allowed to breathe oxygen for a period of time sufficient to wash practically all the nitrogen out of the lungs.   For this period all the expired gases are collected, measured, and analyzed.   Alveolar samples are taken before and at the end of the test.   Cournand et al.,[7] from 158 determinations of the lung nitrogen concentration during room air breathing, concluded that an assumed value of 81% of nitrogen in the lungs before the rebreathing period can be used without introducing a significant error in the final calculation, thus avoiding one of the alveolar samples.

Meneely and Kaltreider[15] found that with the original Christie method the average values of residual air were 292 cc., and with the Lassen et al. modification, 202 cc. higher than with the helium method.

Another factor which introduces errors in the residual air measurements is the nitrogen excreted in the lungs during the rebreathing period.   Darling et al.[9] found that the nitrogen excreted in 7 minutes of breathing pure oxygen averaged 220 cc. in 4 normal subjects, figures which are similar to those obtained by Campbell and Hill.[2]

Cournand, Yarmush and Riley[7] studied the nitrogen excretion on 30 subjects, during 7 minutes of oxygen breathing.   From it they calculated a regression formula for nitrogen excretion.

From this brief review it is clear that the modification introduced into the Christie method makes it more laborious, without correcting completely the discrepancies with the other methods.

The open circuit method, being from a theoretical point of view the best, offers in practice some disadvantages, such as the lack of a graphic record of the expiratory level, and the necessity for extreme accuracy in the nitrogen analysis.

We have endeavored to combine in the Christie procedure the advantage of a large change in the net nitrogen concentration of the alveolar air with that of having a graphic record of the starting expiratory level of the subject, thus making it an exact and simpler procedure for routine measurements.
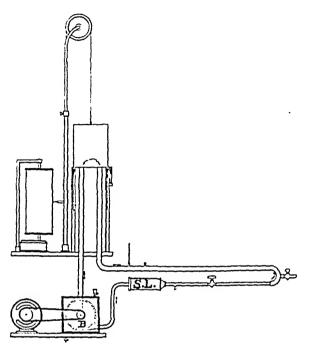

Fig. 1.—Modified Knipping apparatus.   B, Blower; S.L., soda lime container.

Procedure.   The apparatus[3] used was a modified Knipping[12] spirometer of 5 liters capacity (Fig. 1).   The blower was immersed in an oil bath for gas tightness.   The connecting tubes were metallic, and on the inspiratory side there was a soda lime container for carbon dioxide absorption.   A double set of 3-way stopcocks permitted alveolar air sampling, before and at the end of the rebreathing period.   The dead space of the spirometer was 2865 cc., which made the total capacity of the circuit about 8 liters.

The procedure for a determination of functional residual air was as follows: With the blower motor on, the circuit dead space was washed out 10 times with pure oxygen (nitrogen impurities must be known).   Oxygen was then added, usually about 5000 cc. to fill the spirometer bell.   The subject, under basal conditions, was made to breathe through a mouthpiece, and an alveolar sample was taken.   After 2 or 3 minutes the mouthpiece was connected to the spirometer at the end of a normal expiration and a 7 minutes period of rebreathing was allowed; at the end of it, another alveolar sample was taken.

The spirometer and alveolar samples were analyzed in a Shepherd apparatus.   Duplicates checked within 0.10%.   Carbon dioxide content of alveolar specimens was used to detect dilution with dead space gas.

All volume measurements were made from the tracings.   The volume of added oxygen was recorded at the time it was run in, the oxygen consumption was measured from the slope of the tracing.   The initial volume minus oxygen consumption equals the final spirometer volume to which the dead space volume was added.   If needed, temperature corrections were made.

Calculations were made following the original Christie formula (1) and the Lassen *et al.* modification (2).

$$\text{F.R.A.} = \frac{V\bar{p}(\text{Spir.}\bar{p}) - V\bar{a}(\text{Spir.}\bar{a}) - N_2 \text{ excretion}}{0.791 - \text{Spir.}\bar{p}} \quad (1)$$

$$\text{F.R.A.} = \frac{V\bar{p}(\text{Spir.}\bar{p}) - V\bar{a}(\text{Spir.}\bar{a}) - N_2 \text{ excretion}}{\text{alv.}\bar{a} - \text{alv.}\bar{p}} \quad (2)$$

F.R.A. = functional residual air in cc.
$V\bar{p}$ = final spirometer volume plus dead space.
$V\bar{a}$ = initial spirometer volume plus dead space.
Spir.$\bar{p}$ = final spirometer nitrogen expressed as part of an atmosphere.
Spir.$\bar{a}$ = initial spirometer nitrogen expressed in same units (due to impurities in oxygen).
Alv.$\bar{a}$ }
Alv.$\bar{p}$ } = alveolar nitrogen content in same units.

Nitrogen excretion was calculated by the regression formula given by Cournand *et al.* for 7 minutes of pure oxygen breathing.

Nitrogen excretion (cc.) = 96.5 body surf. area (sq.m.) + 35

It was assumed that the nitrogen excretion is proportional to the fall of the gas pressure and that 0.8 of an atmosphere is the change occurring after 7 minutes of oxygen breathing (Darling *et al.*[9]).

The volume of the mouthpiece dead space, 20 cc., was subtracted from the final result. Functional residual air thus obtained may need a correction if the rebreathing period did not begin at the exact end of a normal expiration. Such a correction was determined from examination of the tracing.

Duplicate measurements were made the same morning with a 45 minutes' interval.

Results were corrected to 37° C., and saturation with water vapor.

When measurements with original Christie procedure were made, the apparatus was washed out with room air, and the spirometer bell only was filled with pure oxygen.

McMichael technique was used for hydrogen measurements. The gas samples were analyzed by duplicates in a Shepherd combustion apparatus with an accuracy of 0.10 cc. %.

Results. Subjects were 3 normal males and 14 females with different types of pulmonary lesions without emphysema. Physical characteristics of the subjects are presented in Table 1.

TABLE 1.—PHYSICAL CHARACTERISTICS OF PATIENTS AND NORMAL SUBJECTS STUDIED

Patient	Sex	Age (yrs.)	Stature (m.)	Body surf. area (sq. m.)
A. B.	M	42	1 795	2.09
R. C.	M	23	1.81	1.94
A. F.	M	47	1.68	1 87
A. S.	F	48	1.50	1.42
D. S.	F	39	1.58	1.67
I. G.	F	28	1.52	1.28
M. B.	F	43	1.525	1.26
M. S.	F	39	1.55	1.62
C. S.	F	16	1.62	1.60
C. P.	F	24	1.56	1.59
D. M.	F	28	1.545	1.48
C. S.	F	16	1.62	1.60
L. R.	F	30	1.635	1.77
C. C.	F	28	1.50	1.54
D. F.	F	22	1.575	1 58
R. G.	F	28	1.575	1 43
M. G.	F	35	1 52	1 56

Tables 2 and 3 present in some detail our experimental results. The difference between figures in Columns 3 and 4, giving a measure of the oxygen storage effect are small and negligible in all cases by the authors' technique. It is probably from the trends in our data that with larger volumes of residual air this effect would become significant; it is likewise probable that in the original Christie technique the effect would appear with smaller residual air volumes.

TABLE 2.—FUNCTIONAL RESIDUAL AIR OF PULMONARY TUBERCULOUS PATIENTS, WITHOUT EMPHYSEMA

Subject	Date 1942	Column: 1 Alveolar nitrogen at the end (%)	2 Spirometer nitrogen at the end (%)	3 Christie calculation (cc.)	4 Lassen et al. calculation (cc.)	5 Hydrogen method (cc.)	6 3 minus 4 in % of 4 (%)	7 Difference between duplicates† (%)	8 Maximal difference on same subject† (%)
A. S.	3/13 M	16.90	15.41	1342	...	...	...	0.8	
	3/18	17.16	15.34	1353	...	...	...	...	1.2
D. S.	3/16	18.35	17.36	1459					
	3/17	17.37	15.83	1353				...	7.8
	3/20	17.57	16.48	1370					
I. G.	3/10 M	17.34	15.11	1273			...	3.4	4.9
	3/11	16.74	15.15	1235					
M. B.	3/5	...	14.06	1096					
	3/16	15.86	14.06	1078			...	...	3.5
	3/25 M	13.16	13.03	1106	1073	...	−2.7	1.5	
M. S.	3/30	11.30	10.81	742	731	...	−1.5		5.7
	1/4 M	16.94	10.62	705	69S	...	−1.0	1.0	
C. S.	4/15 M	16.56	15.65	1204	1191	...	−1.7	1.1	5.1
	4/17 M	15.83	14.63	1156	1121	...	−3.1	0.8	
C. P.	4/27 M	15.53	14.93	1146	1109	...	−3.4	7.5	
	4/29	16.72	15.32	116S	1130	...	−3.4	...	8.2
	5/6 M	48.43	57.01	1411	1392				
	5/8	40.13	44.55	1403	1355				
	5/8	15.18	14.88	109S	1068	...	−2.8		
D. M.	4/22 M	19.27	18.3S	1435	1436	...	−0.5	2.1	
	4/24	18.53	16.76	12S4	1316	...	−2.4	...	14.8
	5/4	18.89	17.30	1459	1457	...	−0.1		
	5/4	49.47	47.35	1856	1864				
C. S.	5/29	...	14.14*	...		919			
	5/29	13.94	12.85	903	915	...	+1.3		
	6/1	14.38	12.9S	956	949	...	−0.7		
	6/1	15.28	44.37	1173	1110				
L. D.	6/8 M	18.17	16.15	1303	1303		−0.8	1.9	
	6/9 M	...	12.41*	...		1231			
	6/10 M	49.03	46.78	1550	1503				
C. C.	6/15 M	21.45	18.8S	1816	1625	...	+1.1	0.7	7.5
	6/16	...	13.28*	...	...	139S			
	6/17	...	13.46*	...	...	1619			
	6/17	...	18.2S	1631					
D. F.	7/4 M	...	12.93*	...		1133			
	7/7 M	17.48	14.32	1191	1202		+2.2	2.6	
	7/8 M	46.40	45.54	1434	1445				
R. G.	7/13 M	...	13.60*	...		1117			
	7/14 M	15.40	14.45	1251	1248		−1.6	2.3	
	7/15 M	15.01	14.57	1199	1184		−1.2	2.8	
M. G.	7/17 M	...	15.24	1540				6.7	
	7/20 M	16.93	15.62	1298	1348		+0.8	6.2	25.0
	7/21 M	18.49	15.77	1324	1423		+4.2	5.3	

Figures in italics were obtained with the original Christie method.
* Spirometer hydrogen percentage at the end.
† Calculated from Column 3 values in percentage of the lowest value. Only such of tests' pre results have been included.
M, mean values of duplicate determinations listed for those dates.

TABLE 3.—FUNCTIONAL RESIDUAL AIR OF NORMAL SUBJECTS

Subject	Column: Date 1942	1 Alveolar nitrogen at the end (%)	2 Spirometer nitrogen at the end (%)	3 Christie calcu- lation (cc.)	4 Lassen et al. calcu- lation (cc.)	5 Hydrogen method (cc.)	6 3 minus 4 in % of 2 (%)	7 Difference between duplicates†	8 Maximal difference on same subject† (%)
A. B.	5/18	21.14	21.08	2047	1998	...	−2.5	...	5.1
	5/20	*50.42*	*50.58*	*2402*	*2289*				
	5/21	21.91	21.28	1947	1923	...	−1.2		
	5/21	...	16.21*	...	...	1928			
R. C.	5/22 M	25.44	24.96	2430	2416	...	−0.6	2.5	
	5/27 M	...	15.06*	...	...	2244			
	5/28 M	*51.21*	*51.49*	*2835*	*2707*				
A. F.	6/18 M	23.08	22.39	2142	2047	...	−4.6	5.1	
	6/19	...	13.39*	...	...	2294			
	6/19	...	14.59*	...	...	4176			
	6/22 M	*50.84*	*51.00*	*1765*	*1695*				

Figures in italics were obtained with the original Christie method.
* Spirometer hydrogen percentage at the end.
† Calculated from Column 3 values in percentage of the lowest value.   Only author's technique results have been included.
M, mean values of duplicate determinations listed for these dates.

Nitrogen fall in the alveolar air ranged from 0.55 to 0.69 of an atmosphere with the author's procedure, and from 0.28 to 0.33 with the original Christie method.

Hydrogen concentration was kept between 13% and 15%.

Among both normal subjects and tuberculous patients, duplicate determinations made the same day and on the same subject check within 2.5% as an average.   The checks range from 0.7% to 7.5%. On the other hand, measurements made on different days on the same subject show a maximum difference of from 1.2% to 20% (average 7.9%).

Duplicate measurements by the hydrogen method or by the original Christie method show wider ranges in most cases.

By the hydrogen method, values average 56 cc. lower than our own values.

Using the original Christie technique on 8 subjects, results are, on an average, 215 cc. higher than those calculated with Lassen et al. formula, and the difference ranges from +3.8% to −5.5%. This difference is rather constant when measurements on the same subject are repeated.

Discussion.   From our results it is apparent that, when a large net change in the alveolar nitrogen percentage is produced, and a rebreathing apparatus equipped with a powerful blower is used, the oxygen storage effect as described by Lassen et al.[13] is not present. Such a lack of a storage effect can be explained by the fact that the changes of nitrogen percentage in the inspired gas, produced by oxygen consumption, are lessened by the large volume of the circuit, the low nitrogen concentration, and by the rapid mixing of the gases in the spirometer.

The total volume of the spirometer circuit at the end of the experiment must be at least 3 times larger than the expected residual air, a fact which was already pointed out by Anthony[1] and confirmed by our own measurements.

But even in cases where no oxygen storage effect is present, the determination of residual air volume by using small net changes in alveolar nitrogen content gives higher values than when larger nitrogen changes are used as in the author's technique.

Likewise, Meneely and Kaltreider[15] found higher values with the original Christie method, and Lassen *et al.* modification, than those obtained with the helium method. Furthermore, the results presented in this paper using the hydrogen method agree with those of the author's modified Christie method.

It is then evident that the use of a large net change in the alveolar nitrogen concentration corrects the errors of the original Christie method, errors which the introduction of the alveolar nitrogen percentage in the calculations[13] or the constant volume technique[10] did not remove.

It cannot be decided whether the more correct results are due only to a better mixture of lung gases induced by great differences of the nitrogen pressure (at the start) between alveoli and spirometer or if the final low nitrogen percentage, not magnifying the errors in the calculations and giving a greater sensitiveness to the method, is also an important factor.

That a greater sensitiveness exists is shown by the fact that, using our method, a given change in the volume of the measured residual air induces in the final nitrogen percentage a change 100% greater than using the original Christie method.

The nitrogen excreted by the lungs during the rebreathing period introduces another cause of error in the residual air measurements. The errors by miscalculation of the excreted nitrogen are more conspicuous and significant the smaller the residual air values, and the use of a single correction standard in all subjects, as that obtained from the Cournand *et al.*[7] regression formula, may seem an unjustified assumption. We made also the assumption that the nitrogen excreted would be proportional to the fall in the lung nitrogen pressure.

However, the agreement of our values, even in cases with very small residual air, with those obtained by the hydrogen method, in which the nitrogen is kept at atmospheric pressure during the whole rebreathing period, seems to justify the use of the Cournand *et al.*[7] regression formula. On the other hand, errors by miscalculation of the hydrogen dissolved in the blood are very small.

Only slight differences exist between results calculated by the original Christie formula and by the Lassen *et al.* modification. It appears then that using our technique the original Christie formula may be used without introducing significant errors in the residual air values. Alveolar air samples might then be omitted, and a real simplification could be obtained.

In conclusion, the advantages of the proposed technique for residual air measurements, as they must be done on pulmonary tuberculous patients, are clear-cut. By increasing the net alveolar nitrogen change it offers a better chance of adequate intrapulmonary gas mixing, and it does not magnify the errors in the final result. By avoiding alveolar sampling and extremely low final nitrogen percentage in the spirom-

eter, which would demand very accurate analysis, it simplifies the measurements without introducing significant errors in the results. Finally, the functional residual air values can be corrected for differences in the expiratory level at the start, from the examination of the graphic. Such a correction is particularly useful in cases of nervous patients.

Summary. A modification of the Christie method which makes it suitable for routine examinations, is described. Errors are minimized by increasing the change in concentration of the alveolar nitrogen. Alveolar sampling is avoided, analysis need not be so accurate. A graphic record of the expiratory level is obtained. Results on 14 tuberculous patients without emphysema and 3 normal subjects were compared with those obtained by the original Christie method and the McMichael hydrogen method. The significance of the results is discussed.

REFERENCES

1. ANTHONY, A. J.: Ztschr. f. d. ges. exp. Med., **104**, 623, 1939.
2. CAMPBELL, A. J., and HILL, L.: J. Physiol., **71**, 309, 1931.
3. CHIODI, H.: Public. del Centro de Inv. Tisiológicas, **4**, 59, 1940.
4. CHRISTIE, R. V.: J. Clin. Invest., **11**, 1099, 1932.
5. COURNAND, A., DARLING, R. C., MANSFIELD, J. S., and RICHARDS, D. W., JR.: J. Clin. Invest., **19**, 599, 1940.
6. COURNAND, A., BOLDWIN, E. De F., DARLING, R., and RICHARDS, D. W., JR.: J. Clin. Invest., **20**, 681, 1941.
7. COURNAND, A., YARMUSH, I. G., and RILEY, R.: Proc. Soc. Exp. Biol. and Med., **48**, 280, 1941.
8. DARLING, R. C., COURNAND, A., and RICHARDS, D. W., JR.: J. Clin. Invest., **19**, 609, 1940.
9. DARLING, R. C., COURNAND, A., MANSFIELD, J. S., and RICHARDS, D. W., JR.: J. Clin. Invest., **19**, 591, 1940.
10. HERRALD, F. J. C., and McMICHAEL, J.: Proc. Roy. Soc., London, Ser. B, **126**, 491, 1939.
11. KALTREIDER, N. L., FRAY, W. W., and HYDE, H. V.: Am. Rev. Tuberc., **37**, 662, 1938.
12. KNIPPING, H. W., and RONA, P.: Prak. d. Phys. Chem., **3**, 143, 1928.
13. LASSEN, H. C. A., COURNAND, A., and RICHARDS, D. W., JR.: J. Clin. Invest., **16**, 1, 1937.
14. McMICHAEL, J.: Clin. Sci., **4**, 167, 1939.
15. MENEELY, G. R., and KALTREIDER, N. L.: Proc. Soc. Exp. Biol. and Med., **46**, 266, 1941.

DIABETES AND THE WEATHER

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IN a recent paper Beardwood and Rouse,[1] studying the onset of diabetic coma in 220 cases, found that in 100 of them no obvious cause was to be ascertained. In a later paper, Joslin, Root, White and Marble[3] came to the conclusion that the "commonest cause of diabetic coma

continues to be laxity in treatment consisting either of dietary indiscretions or neglect to take an adequate amount of insulin, or both."

This point is driven home with the clinical demonstration that with prompt and proper dosage of insulin, fluid, and salts, the coma can be overcome.

The situation, however, is not as simple as might therefrom be inferred. Every physician who has followed his cases carefully and whose patients have followed routine instructions faithfully is confronted, as Beardwood and Rouse make evident, with the sudden precipitation of coma, and both physician and patient cannot adequately explain the reason.
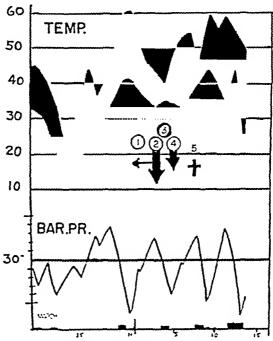
FIG. 1.—Meteorogram to illustrate the clinical events in Case 1 of Drs. Joslin, Root, White and Marble.

Before proceeding to the rather involved discussion, I shall examine 3 case reports detailed by Dr. Joslin and his associates, to illustrate a very simple association of the condition of the patient to the environmental situation which may play a rôle in aggravating the picture.

Joslin's Case 1 was moribund when first seen on April 3, 1910 (episode [2] in Fig. 1). The history indicated that he had eaten little or nothing for 3 days previously (1). After improvement the patient again became drowsy (3, 4); then improved, but died suddenly on the 5th of April (5). When we examine the meteorogram (Fig. 1) for the period under consideration we observe the following: Environmental temperatures had been relatively high at the end of March, barometric pressures had been low and with the passage of this cyclonic

air mass, rain had fallen. Then followed a polar episode—temperatures declined to 40° F., a barometric crest obtained when the patient was first seen. Sudden death occurred with the next barometric crest. We turn to the next 2 cases (Fig. 2) and immediately note that these 2 patients died at approximately the same time (August 24 and 25). Such coincidence is accepted as chance. But is it? According to the record, Patient No. 2 was admitted on August 13 and Patient No. 3 on August 17, both in acidosis, although the exact time of the onset was not indicated in the record.
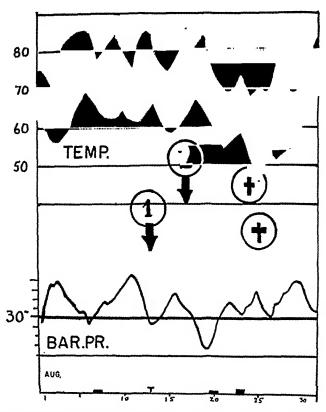
FIG. 2.—Meteorogram to illustrate the clinical events in Cases 2 and 3 of Drs. Joslin, Root, White and Marble.

When we now examine this meteorogram we note that death occurred when temperatures had fallen from maxima in the eighties to lows in the forties and air pressure had increased to a crest.

Do such environmental situations alter the metabolism of the healthy or diabetic individual and do they play a rôle in precipitating acidosis?

The Exceptional Requirement of Insulin and Salt Solution in Diabetic Coma. In Root and Riseman's[7] interesting study of the use of insulin and salt solution in diabetic coma, 2 case reports have been dated: The first concerned a woman, 31 years of age, who was admitted to the Beth Israel Hospital in Boston on April 22, 1937 (episode [3] in Fig. 3). Four days previously she had lost her appetite (1), and 2 days previously she had been short of breath and vomited (2). On the morning of admission she was found unconscious.

Examination of the meteorogram (Fig. 3) immediately indicates the onset of the disturbance when temperatures had fallen from a maximum of 70° to 35° and an increase in the severity of the symptoms (hospitalization) occurred with the succeeding barometric crest and fall in temperature.
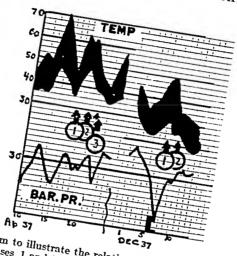

FIG. 3.—Meteorogram to illustrate the relation of coma and the clinical course in Cases 1 and 2 in Root and Riseman's report.

In the second case described, a teacher, 25 years of age, who was a diabetic, had been taking 50 units of protamine zinc insulin to September 4. On December 7 she felt as if she were getting a mild attack of grippe (episode [1] of second case in Fig. 3) and from 10 o'clock on she vomited every 10 minutes. She was admitted to the hospital at 5 P.M. on December 8 quite unconscious (2.)

Examination of the meteorogram immediately indicates the association of the entire clinical episode with the passage of a sharp polar front, 3 in. of precipitation having occurred on the 6th of the month, more than ½ in. on the 7th and barometric pressures increased more than 1 in. in 2 days' time!

Organic Variability. For the complacent acceptance of a static rather than a dynamic concept of the human organism (the interested reader might turn to Lawrence Henderson's[2] discussion of this subject), Cannon's term "homeostasis" provided an assurance that was apparently very satisfying. There can be no question of its general validity, but within this framework there appears a wide latitude of chemical movement and when we study the biochemistry or the physiologic function of the normal or sick human we find that the organism is never the same from day to day.

Every passing phase of sympathicotonia, with its increase in diastolic and systolic blood pressure, is associated with a transient anoxia (largely peripheral), this involves the production of more acid products because of the anoxybiosis. Tissue stimulation follows, and is reflected in the capillary bed with an increase in permeability, and this, in turn, is associated with greater tissue hydration. But every passing phase of sympathicotonia is also associated with sugar mobilization

from the liver stores of glycogen and this sugar is released at a time when the peripheral bed (skin, muscles, connective tissue) is relatively constricted and the mobilized sugar cannot be delivered to the areas where most of it would be utilized under normal conditions, provided adequate insulin were available.

Any sympathicotonia therefore tends to accentuate the diabetic state; when repeated in rapid sequence or when amplified because of violent environmental changes, a background is laid for diabetic coma.

Cold, relative or actual; hyperventilation; undue excitement; any infection or trauma; any sudden disturbance of metabolic equilibrium (Hippocrates) throws a greater burden on mechanisms of autonomic equilibration, and in so doing precipitates a diabetic crisis.

Obviously insulin dosage must be such that it provides a wide margin of safety for these constant pendulations and amplifications of the organic tide. When the margin of adequacy is restricted, a seemingly minor change in the environmental condition may be followed by disaster. It is for this reason that the commonplace changes in the environment associated with weather and season must be seriously drawn into the sphere of interest of the attending physician and the patient.

To illustrate this I turn to a simple example from the records of the Children's Memorial Hospital, generously placed at my disposal by Dr. Newcomb.

The cases admitted in coma for the year 1932 are indicated in Table 1 and it will be observed that 3 young children were admitted in coma at the same time (February 2 and 4). Why the sudden precipitation of an acute condition?

TABLE 1.—ONSET AND HOSPITAL ADMISSION DATES OF DIABETIC CHILDREN (1932)
(Dr. Newcomb)

Name	Sex	Dur. of disease on admission (wks.)	Age at onset	Date of onset	Admission
S. O. . . .	F	3	2–10	1–13–32	2– 2–32
D. S. . . .	M	2	2– 4	1–21–32	2– 4–32
D. O. . . .	M	1	2– 3	1–27–32	2– 2–32
D. K. . . .	F	8	8– 5	2–21–32	4–21–32
B. B. . . .	F	16	11– 9	5– 2–32	8–16–32
D. N. . . .	M	8	2– 0	5– 5–32	7– 5–32
F. W. . . .	M	2	1– 3	7–14–32	7–28–32
K. C. . . .	M	20	8– 3	7–20–32	12–20–32
A. L. . . .	M	2	1– 2	9–10–32	9–24–32
R. R. . . .	F	3	2–10	10– 6–32	10–27–32
G. H. . . .	M	3	8– 0	10–15–32	11– 8–32
E. S. . . .	M	3	11–11	10–21–32	11–12–32
E. B. . . .	M	2	8– 9	12–15–32	12–29–32

We turn to examine the meteorologic situation at the time as illustrated in Figure 4. It will be observed that temperatures declined from 50° F. to 0° on January 31. Then temperatures rose abruptly. With such a situation a relative anoxia can readily be demonstrated in the normal as well as in the sick individual. The peripheral blood bed tends to close, sugar is mobilized, it is kept from the periphery at the same time that acid metabolites accumulate. After this phase, vessels become more permeable, tissues swell, in the potential or actual diabetic coma can develop. (Arrows A and B, February 2 and 4.)

When we examine the day by day records of diabetic deaths for Chicago at the time when this episode occurred in children we can observe a characteristic crest in the number of deaths. In other words, the sudden precipitation of diabetic coma in these young children was not a chance phenomenon, others in the diabetic population were also involved.
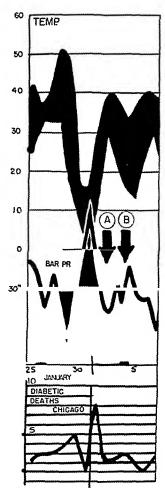

FIG. 4.—Meteorogram to illustrate death episodes discussed in Dr. Newcomb's Table of Admissions of Diabetic Children. Upper curve, maximal and minimal temperatures; heavy solid curve, barometric pressures; lowest curve, daily diabetic deaths. Chicago records for the period.

Variability of Sugar Output in the Diabetic. Among the curious phenomena of diabetes that interested Naunyn, the founder of our modern knowledge of diabetes, was the obvious fluctuation in the sugar output in the diabetic who was kept on an absolutely controlled sugar régime. Naunyn[4] could not account for it. I shall illustrate his findings by introducing one of his own controlled observations, using his original chart. (Fig. 5.)

To make the association of decrease in environmental temperatures and increase in sugar output readily evident I have merely numbered a few of the outstanding periods (circled numbers 1 to 10) on both curves.

During August, two major polar air masses swept over Strassburg (1) and (2). The increase in barometric pressure and fall in temperature is readily apparent. To this change the two sugar crests (1) and (2) are related.
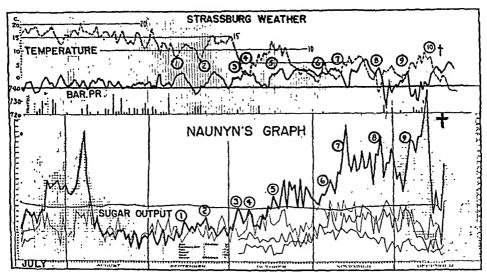

FIG. 5.—Naunyn curve of sugar output with superimposed meteorogram for Strassburg. Naunyn's curve of sugar excretion in a patient observed in Strassburg from July 14 to his death on December 19. Controlled regimen became effective about August 10. Increased excretion occurred in short waves of approximately 4 to 5 days' duration. Major increase began early in October. Dotted line, mean daily temperature in centigrade; solid line, barometric pressure in millimeters; black columns, precipitation.

Early in October (3) and (4) an increase in sugar output is again apparent. Environmental temperatures fell from 15° C. to 0°. With this the sugar curve rose sharply and on October 16th barometric pressures again rose abruptly—a sugar crest was evident on the 17th (5). A temperature decline then followed from the 17th for the balance of the month and sugar levels remained high. A crest on November 3d followed episode (6).

In this fashion each major environmental change finds its reflection in change in the sugar level reflecting a mobilization and a distribution and the accumulation of sugar as the result of defect in utilization. In this case the final sugar crest occurred on December 13th, following an increase in barometric pressure from the lows of December 10th and 11th. The patient then died with the further development of the cold wave.

Discussion and Summary. The interrelation of environmental temperature and air pressure and the underlying biochemical changes that occur in the human have been discussed in detail in a recent publication (5), and the diabetic problem has been discussed fully elsewhere.[6]

The clinical inference might seem obvious, namely, fortifying the patient by increasing the insulin intake with changing seasonal and weather demands. The intelligent patient can be instructed to modify the dosage with change in weather. Possibly even more important is the recognition of the hazard involved in adjustment to cold and the consequent instruction of the patient to promptly make use of adequate clothing, suitable room temperatures, the avoidance of unnecessary exposure and taxing environmental situations of whatever nature. The same physiologic adjustment that occurs with cold is basically involved in fear and anger or excitement, in the early stages of infection, in gastro-intestinal overload, in allergic reactions, in pain, and finally in fatigue.

REFERENCES

1. BEARDWOOD, J. T., and ROUSE, G. P.: J. Am. Med. Assn., 117, 1701, 1941.
2. HENDERSON, L. J.: Science, 9, 1, 1941.
3. JOSLIN, E. P., ROOT, H. F., WHITE, P., and MARBLE, A.: J. Am. Med. Assn., 119, 1160, 1942.
4. NAUNYN, B.: Der Diabetes Mellitus, Vienna, Holder, 1898.
5. PETERSEN, W. F.: Arch. Biochem., 1, 269, 1942.
6. PETERSEN, W. F.: The Patient and the Weather, vol. 4, P. II, Ann Arbor, Mich., 1937,
7. ROOT, H. F., and RISEMAN, J. E. F.: J. Am. Med. Assn., 110, 1730, 1938.

PRECLINICAL GENITO-URINARY TUBERCULOSIS

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RICORD's classification of the luetic infections into primary, secondary and tertiary stages was so striking and fundamental that it probably influenced Ranke to apply similar categories to tuberculosis (1916). To substantiate this thesis Ranke could point to Naegeli's postmortem findings (1900), v. Pirquet's doctrine of allergy (1906), and Ghon's study of the character of the primary infection (1912). Since then phthisiologists are agreed that in tuberculosis there are 3 stages of development: the analogy with syphilis is basically correct. However, chronologically, the succession of the stages is *not* always I, II, III, in a forward progression as Ranke taught. Stage I can become III without an intermediate hematogenous dissemination (II), and an isolated organ tuberculosis (III) can give rise to recurring or a single episode of II. Ranke's classification restricts the evolutionary possibilities in a given individual. Tuberculosis is more dynamic

TABLE 1.—CLINICAL SUMMARY OF CASES

Case	History	Pulmonary status, other diagnoses	Urine	PSP (%)	Conc.	Urologist's impression
M. 49 Japanese Male	6 mos.; pleurisy, effusion, gonorrhea	IIA, sputum pos.; pleurisy with effusion, bilateral	Alb. 2+ Incr. WBC RBC Pos. cult.: 4 of 7	92	1006–30	Tuberc. prostatitis and epididymitis; calcific. in right kidney; tuberc. of left kidney
W. 28 White Female	6 mos.; pleurisy, effusion	No parenchymal disease; resolved pleural effusion, right	Alb. tr. to 1+ Pos. cult.: 1 of 3	..	1014–25	Negative
M. 34 Philippine Male	10 mos.	IIC, sputum pos.; left pleural effusion	Alb. 4+ Incr. WBC Hematuria Pos. cult.: 2 of 2	50	1006–24	Tuberc. of left kidney; ulceration of bladder with perforation
N. 23 Negro Male	2 yrs.	IIA, sputum pos.; right hydropneumothorax	Alb. tr. RBC Pos. cult.: 1 of 7	..	1015–20	Negative
T. 25 White Male	1 yr.	IA, sputum neg.; bilateral pleural thickening	Alb. tr. to 2+ Incr. WBC Pos. cult.: 2 of 2	80	1005–15	Cystoscopy: neg.; intraven.pyelography: dis. of left kidney; postop. specimen; caseous-ulcerative tuberc. left kidney
R. 43 Negro Male	3 yrs.	IIIB, sputum pos.; hematogenous infiltration of the lungs; brain tuberculoma (?); Pott's disease	Alb. 2+ Incr. WBC RBC Pos. cult.: 3 of 3	96	1013–20	Cystoscopy: granulation tissue throughout lower half of bladder, ureters contracted, questionable patency on right; retrograde: left kidney disease
H. 21 Negro Male	4 mos.	IB, sputum pos.; bronchial lymph node penetrating into bronchus; tuberculosis of both knees; Pott's disease	Alb. 2+ Incr. WBC Pos. cult.: 2 of 6	89	1026–33	Epididymo-orchitis left; postop. specimen: same; cystoscopy: neg.; pyelography: right kidney disease
N. 24 White Male	13 mos.	IIB, sputum pos.	Alb. tr. Pos. cult.: 1 of 1	..	1014–22	Negative
R. 22 White Female	13 mos.	IA, sputum neg.; bilateral pleural thickening	Alb. tr. Pos. cult.: 1 of 6	..	1010–25	Negative
M 43 Negro Male	10 mos.	IA, sputum neg.	Alb. 2+ Incr. WBC RBC Pos. cult.: 2 of 5	88	1008–27	Negative
V. 20 White Male	3 wks.; pleurisy, effusion, right	No parenchymal disease; thickened pleura, right	Alb. Incr. WBC Pos. cult.: 5 of 5	96	1014–22	Cystoscopy: granulation tissue and ulceration at both ureteral openings, more so at right; pyelography: left kidney disease; postoper. specimen: caseous tuberc. of left kidney and ureter
R. 19 White Male	3 mos.	IIA, sputum pos.	Alb. tr. Incr. WBC Pos. cult.: 0 of 3	..	1010–26	Epididymitis, right
M. 24 White Male	7 yrs. "pleurisy"	IIB, sputum pos.	Alb. tr. Incr. WBC Pos. cult.: 2 of 4	58	1014–27	Cystoscopy: scarring and constriction of left ureteral opening; intraven. pyelography: disease of left kidney
M. 19 White Male	5 mos.	IIB, sputum pos.; hematogen. infiltration in lungs; calcification in mesenteric lymph nodes	Incr. WBC Pos. cult.: 3 of 3	43	1005–23	Cystoscopy: neg.; pyelography: left kidney disease; postop. specimen: caseous ulcerative tuberculosis
B. 17 Colored Male	5 mos.	Penetrating bronchial lym. node, terminating in miliary dissemination and penetration into heart	Alb. 2+ Incr. WBC Pos. cult.: 2 of 3	..	1024–26	Negative; postmortem: miliary tubercles throughout all organs, Pott's abscess, caseous tuberculosis of heart

in its course than is pictured in his straight line sequence of stages. Figure 1 would be more characteristic of the changes that can occur.

I → II → III   primary focus I→III   organ tuberculosis
   (Ranke)   (alternative)   ↘↙↗
                                        II
                                  dissemination

FIG. 1.—Stages occurring in tuberculosis, Ranke and alternative sequences.

With this scheme in mind, it will be realized that tuberculous disseminations can be a frequent possibility. Consequently, the eagerness to diagnose extra-pulmonary foci should be as keen as our endeavors in any pulmonary survey. The urine offers a ready and adequate source for the investigation of genito-urinary tuberculosis, and here the laboratory can ever be the first to report an excretory tuberculosis. A normal urine in the female contains up to about 12 WBC per high-power field per centrifuged specimen of 15 cc., in the male up to about 6. In a tuberculous individual any increase in the number of the pus cells or the presence of red blood cells or albumin should automatically call for a 24-hour specimen to be concentrated for tubercle bacilli. The smear from such concentration allows only a preliminary report. As a routine, the residue should then be treated and cultured on a standard medium for tubercle bacilli. Such concentrates and cultures of 24-hour specimens are to be repeated monthly or bi-weekly until a sufficient number of reports are available for the urologist to plan his cystoscopic and retrograde examinations.

This is the routine employed at the Municipal Sanatorium. Our institution has been receiving minimal and moderately advanced cases* of pulmonary tuberculosis from the clinics and hospitals of the City of New York. Since the induction of our urine routine, we have uncovered a relatively high percentage of excretory tuberculosis. The high figure occurring in a sanatorium population with comparatively little chest disease emphasizes the necessity of being on the alert to diagnose latent or preclinical genito-urinary tuberculosis.

Data. During August, 1940 to February, 1942, 393 24-hour urine specimens were studied for tubercle bacilli because routine specimens from the same patients revealed contents deviating from the absolute normal. These came from 214 different individuals. Tubercle bacilli were isolated in 29 instances, representing 14 individual cases. One individual had definite clinical evidence of a tuberculous orchitis, yet urine specimens were persistently negative for tubercle bacilli. Thus, of 214 suggestive cases, 15, or 7% yielded positive clinico-pathologic findings (Table 1). The positive cases comprised 2 yellow males, 5 negro males, 6 white males, and 2 white females. Their ages varied from 17 to 49. Of these individuals, 3 gave a definite history of pleurisy with effusion, 1 claimed to have had "pleurisy," 1 developed a pleurisy with effusion under observation, and 2 showed evidence of thickened pleuræ roentgenographically or radiographically. Three cases had

* In 1941, 557 admissions, of which 51.4% were classified as minimal, 41.6% moderately advanced, and 3.4% far advanced. The remainder were non-tuberculous.

chest films characteristic of a hematogenous dissemination through the pulmonary circuit, and 4 had simultaneous bone lesions (3 Pott's, 1 knee). Table 2 gives the distribution of the genito-urinary pathology in our group.

TABLE 2.—GENITO-URINARY TUBERCULOSIS

I. Renal:
    Kidney and ureter 9
    Bladder 4
II. Genital:
    A. Male—
        Prostate 1
        Epididymis 3
        Testis 1
    B. Female—
        Uterus . . . .
        Ovaries and tubes . . . . .
III. Tuberculous bacilluria 5

The conclusion of 7% was derived from the ratio of 15 positive cases to the 214 studied. During this interval of time, 1230 individuals were treated at the sanatorium. Thus, considering the total population, the percentage of genito-urinary tuberculosis was 1.2%.

All organisms isolated were identified bacteriologically by their cultural characteristics and by guinea pig inoculations. From 1 woman a positive culture was subsequently identified as a smegma organism. The occurrence of non-tuberculous acid fast organisms in our survey was 1:29.

Clinical Course. Clinically, our cases can be divided into 3 separate groups:

1. *Clinical Genito-urinary Tuberculosis.* These were the cases which offered frank clinical signs: pyuria, hematuria, dysuria, enlarged testicle, or epididymis, etc. Tubercle bacilli were abundant and already in the plain smear of the 24-hour specimen. The patients had complaints, the clinical and laboratory findings were many.

Case Histories. V. 29, white male. In 1939 pleurisy with effusion which was tapped. In 1940 gradual onset of pain and burning on urination, frequency. Urine showed albumin. Urine cultures positive for tubercle bacilli; later smears of concentrates positive on direct examination. Cystoscopy: granulation tissue and ulceration at both ureteral openings, more so at right. Pyelography: left kidney disease. Nephrectomy performed. Specimen showed caseous-ulcerative tuberculosis of kidney and ureter.

M. 34, Philippine male. Had been admitted to another institution because of urinary distress but "work-up did not exclude the possibility of tuberculosis." Admitted to Otisville for chest condition and complaints of dysuria, frequency, and hematuria. Urine: alb. 4+, RBC, numerous WBC/HPF. Cystoscopy: ulceration of bladder and scarification of left ureter. Subsequent course: development of urinary retention, onset of abdominal tenderness. Laparotomy performed: perforation of posterior wall of bladder, tuberculous peritonitis. Transferred to the City. Left nephrectomy done. Patient recovered from the acute bladder disease.

2. *Subclinical Genito-urinary Tuberculosis.* On the other hand, there were the cases in which symptoms and complaints were vague or absent. Because of some abnormal content of the urine, 24-hour

specimens were cultured and tubercle bacilli found. Successive positive findings set the indication for cystoscopy and pyelography which revealed conclusive pathology.

These are the cases which were discovered early, and they differ from clinical genito-urinary tuberculosis only in degree and extent. All tuberculosis begins as minimal disease, and timeliness of diagnosis is desirable also in genito-urinary tuberculosis.

TABLE 3.—REPORTS ON GENITO-URINARY TUBERCULOSIS

Author		Type of material	Incidence of genito-urinary pathology		%
Harris	1930	Tuberculous bone lesions	16 of	43 adults	37
			9 of	67 children	13
Bumpus	1930	Urine from supposedly normal contralateral kidney	43 of	175	25
Rieder	1931	Mod. and far adv. cases	11 of	136	8
Menton	1932	Mod. and far adv. cases	1 of	76	1.3
Band	1935	Patients with extrapulmonary tuberculosis	25 of	174	14
Munro	1935	Mod. and far adv. cases	22 of	160	14
Saenz, etc.	1935	Mod. and far adv. cases	0 of	100	
Mack	1937	Patients with extrapulmonary tuberculosis	15 of	20	75
Miller, etc.	1939	General tuberculosis population	84 of	1316	6.6
Rosencrantz	1940	Mod. and far adv. cases	14 of	200	7
Morse, Scott	1940	General tuberculosis population	76 of	2049	3.8
Auerbach	1940	Autopsy material	127 of	1143	11

* Correspondence with the authors corrected this percentage from 28.

Case Histories. T. 25, white male. Admitted for chest condition. Urine: alb. 2+. Positive cultures. Intravenous pyelography revealed disease of left kidney. Nephrectomy performed and specimen showed caseous-ulcerative disease of left kidney.

M. 49, Japanese male. Past history of pleurisy with effusion, and gonorrhea. Urine on admission contained 2+ alb., clumps of WBC, and RBC. Urine cultures for tuberculosis set up. In view of history, an intermittent discharge was investigated for gonorrhea. Cultures positive on two occasions, complement fixation for gonorrhea: 5.9. Patient given several courses of sulfathiazole. Of 7 cultures for tubercle bacilli, 4 became positive. Pyelogram showed calcification in *right* kidney. Split specimens revealed tubercle bacilli coming from *left* kidney (positive culture and positive guinea pig inoculation). Diagnosis: calcified foci in right kidney, active focus in left; tuberculosis prostatitis activating old gonococcal infection. Transferred to city, where *tuberculous* epididymitis uncovered. Epididymectomy performed.

3. *Tuberculous Bacilluria, Occult Genito-urinary Tuberculosis.* Here again the indication for urologic examination was set by the laboratory. The excretion of tubercle bacilli was not constant, and clinical investigation could determine no causative pathology. Apparently, function was normal, and evidence of morbid change could not be revealed by the urologist. Yet, we must assume that a focus, or several foci, and these even bilaterally, had been established during Phase II of the patient's tuberculous history. When the foci heal, and they will heal as completely as do similar foci in the lungs,[1,3,6,7] the bacilluria is transitory. On the other hand, the foci may go on to ulceration and the case then becomes one of subclinical genito-urinary tuberculosis. These cases require constant check in order that surgical intervention be instituted before the appearance of frank clinical signs.

Case History. Five of our 15 cases were of this type. Anatomic pathology was not found, yet because of the repeated isolation of tubercle bacilli the literature has taught us to interpret these as authentic instances of renal tuberculosis. They are, then, the minimal cases heretofore overlooked unless "they had good luck to have their renal tuberculosis discovered in the preclinical or occult stage because they happened to be selected for inclusion in a research or enjoy the services of an exceptionally thorough clinical pathologist" (Dukes[4]). Whereas, the common location of an occult focus is in the kidney, the epididymis, etc., should not be overlooked.

Whereas *clinical* and *subclinical* excretory tuberculosis differ only in the extent of the symptomatology, we endeavor to stress the importance of the *tuberculous bacilluria* by grouping it with SUBCLINICAL form into PRECLINICAL genito-urinary tuberculosis.

Discussion. Pulmonary tuberculosis is very frequently complicated by urogenital tuberculosis (Table 3), in fact, more so than is generally accredited. Unfortunately, the diagnosis of urogenital tuberculosis is very often missed in the first stage of the disease because of its asymptomatic course.

The Pathogenesis of Urogenital Tuberculosis:
1. *Ascending*—mechanical factors or from the prostate.
2. *Direct Extension*—from the neighboring organs.
3. *Lymphatic.*
4. *Hematogenous*—the most frequent.

The most usual method of renal infection is by the hematogenous route. Renal tuberculosis is never a primary lesion but a complication of a tuberculous process localized elsewhere, the renal infection occurring when the primary focus in the body has already manifested itself. Renal tuberculosis as a hematogenous complication of this primary focus arises when the tubercle bacilli localize in the renal cortex and cause a simultaneous infection in both kidneys.[1,3,5,6] These foci may heal just as primary foci in the lung heal. When these foci break down, active renal tuberculosis occurs, the tubercle bacilli enter the urinary tubules and appear in the urine. "As the infection spreads, caseous foci are formed in the medullary pyramids and give rise to ulcerations of the overlying epithelial lining of the calyces in the renal pelvis, as a rule involving only one kidney."[5]

Secondly, in the evolution of an individual's disease, tuberculosis of any organ can break down and disseminate tubercle bacilli *via* the blood stream and set up a renal infection even after the individual had reached the tertiary period of Ranke (Fig. 1). Thus, excretory tuberculosis should be expected as a frequent occurrence.

A minority of authors contend that the tubercle bacilli may pass through a non-diseased kidney. However, generally authors believe that the finding of tubercle bacilli in the urine is indicative of renal tuberculosis provided that the genital system is ruled out. This conclusion has been borne out by a number of experiments. Medlar and Sasano[7] inoculated guinea pigs with tubercle bacilli, examined the urine, sacrificed the guinea pigs and demonstrated that in all cases showing tubercle bacilli in the urine, kidney pathology was always found. Munro and Bond studied 5 cases of bacil-

luria with no symptoms during life. In all 5 cases tuberculous foci were found in both kidneys. Spitzer and Williams[9] inoculated 103 guinea pigs with normal urine from patients with pulmonary tuberculosis. All pigs remained normal. However, in another series of 106 cases, 4 of the urinary specimens contained albumin, casts, or white blood cells. Of these, 4 of the guinea pigs died of tuberculosis.

"A true tubercle bacilluria does not exist, as an impartial review of the evidence in favor of and against such an occurrence reveals. The presence of tubercle bacilli in the urine signifies a specific lesion; and the ability to demonstrate it by clinical and laboratory methods is possible in practically all cases if they can be kept under observation sufficiently long."[5]

Morse and Scott[8] for the past 9 years routinely examined the urine of every patient in the Manitoba Sanatorium (2409). A culture of the urine was made in any case showing pus, albumin, or red blood cells. If the culture was doubtful, a guinea pig inoculation was carried out. These authors found that in 76 cases (3.8%), tubercle bacilli were present in the urine. Forty of the 76 cases had pulmonary tuberculosis, 12 had osseous lesions. In 5 cases, no extra-renal tuberculosis could be found. Nineteen patients had a bilateral involvement.

Our experience is reported to stress the frequency with which excretory tuberculosis can be uncovered in patients with comparatively little chest disease and without renal symptomatology. The tuberculous bacilluria is as important as the more advanced stages, for thus, an adequate régime can be instituted to treat the renal infection and progression to an unfavorable degree possibly avoided.

Beach and Schultz[2] followed 8 patients over different periods of time because varying numbers of pus cells and erythrocytes were found in bladder urine specimens. This follow-up over 8 to 15 years revealed that objective or subjective symptoms have not returned and in their absence the authors conclude that the tuberculous renal pathology from which these persons suffered at first has healed. The cases are reported in support of the contention that clinical healing of early renal tuberculosis does occur, especially if cessation or extensive anatomic changes have not occurred.

Conclusions. 1. Urinary findings of an increased number of white blood cells, albumin, or blood in a tuberculous individual should cause investigation for genito-urinary tuberculosis.

2. Concentrates of 24-hour urine specimens for tubercle bacilli supplemented by culture methods should be routine in every tuberculosis institution.

3. In a sanatorium population with comparatively little chest disease, of 214 cases investigated for excretory tuberculosis, 15 (7%) gave positive findings. Of these, 5 were in the form of a tuberculous bacilluria.

4. Genito-urinary tuberculosis can be divided into 3 clinical forms: (a) *Clinical*—symptoms are frank and many, pathologic change is obvious; (b) *Subclinical*—in which laboratory findings set the indications for urologic work-up; pathologic condition is then uncovered; (c) *Tubercu-*

lous bacilluria—the form in which urine cultures for tubercle bacilli are positive, yet pathologic change though present, is not manifest.

5. *The tuberculous bacilluria* and the *subclinical form* have been grouped together into *preclinical genito-urinary tuberculosis*.

REFERENCES

1. AUERBACH, O.: New Internat. Clin., 3, 21, 1940.
2. BEACH, E. W., and SCHULTZ, W. G.: J. Urol., 46, 590, 1941.
3. DIMTZA, A., and SCHAFFHAUSER, F.: Ztschr. f. Urol., Chir., 35, 440, 1932.
4. DUKES, C. E.: Brit. Med. J., 10, 799, 1939.
5. EISENDRATH, D. N.: Surg., Gynec. and Obst. Supplement, 66, 67, 1938.
6. LIEBERTHAL, F., and HUTH, V.: J. Urol., 30, 153, 1933.
7. MEDLAR, E. M., and SASANO, K. T.: Am. Rev. Tuberc., 10, 370, 1924.
7a. MEDLAR, E. M., and ORDWAY, W. H.: J. Am. Med. Assn., 119, 927, 1942.
8. MORSE, H. D., and SCOTT, D. L.: Canad. Med. Assn. J., 42, 424, 1940.
9. SPITZER, W. M., and WILLIAMS, W.: J. Am. Med. Assn., 88, 1870, 1927.

STUDIES ON 2-SULFANILAMIDO-4-METHYL-PYRIMIDINE (SULFAMERAZINE, SULFAMETHYLDIAZINE) IN MAN

III. THE TREATMENT OF MENINGOCOCCIC MENINGITIS.*

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SULFAMERAZINE (2-sulfanilamido-4-methyl-pyrimidine), synthesized by several groups of investigators,[8,10] is one of several methyl homologues of sulfadiazine. The pharmacologic and toxicologic behavior of this compound in laboratory animals,[11] and its therapeutic efficacy against a variety of experimental infections[8] suggested that this drug had definite clinical potentialities. Studies in man have shown that higher blood levels are attained more rapidly and are sustained for a longer period of time following the oral administration of sulfamerazine than after the ingestion of similar amounts of sulfadiazine.[5,6] Results of preliminary studies suggest that the toxicity of sulfamerazine to man is comparable to that of the sulfonamides in common use at the present time.[2]

These studies of the behavior of sulfamerazine suggested that its use in the treatment of meningococcic meningitis might prove advantageous. This disease was epidemic in Philadelphia in the past winter

and ample opportunity was provided for the clinical trial of sulfamerazine.   Up to the time of writing, 45 patients, suffering from meningococcic meningitis,* have been treated with sulfamerazine.† The relevant data are shown in Table 1.   Thirty-six of the patients were adults, ranging in age from 13 to 77 years, and the remaining 9 were children of 1 to 11 years. All were gravely ill and presented typical clinical manifestations of meningitis.   The cerebrospinal fluid was turbid in every instance but one (Case 13), in which the lumbar puncture was performed 8 hours after onset of symptoms. Bacteriologic studies were made throughout the investigation. Spinal fluid cultures were positive for the meningococcus in all but 7 cases and in these the diagnosis was supported by the finding of typical organisms on direct smear.   No explanation for our failure to obtain growth in these 7 cases is available. In most instances, a luxuriant growth was obtained within 16 hours.   On the basis of our experience this favorable result was due in a large measure to the routine use of capneic incubation.[8] Blood cultures were made routinely and meningococci were found in 8 cases (17.8%).

In general, the following dosage of sulfamerazine was employed. The initial dose was always given intravenously as sulfamerazine sodium (5% solution in sterile distilled water), adults receiving 3 gm. and children 1 to 2 gm.   This dose was immediately followed by sulfamerazine orally, adults receiving 1 gm. every 4 hours, children receiving 0.25 gm. to 1 gm. every 6 hours.   In delirious or comatose cases the drug was administered by nasal tube until the patient was capable of taking medication by mouth. Sulfamerazine dosage was continued in full amounts, unless toxic manifestations developed, until the patient appeared entirely well clinically.   In the successfully treated group the average total dosage of the drug for the adults was 56.4 gm., given over an average period of 9.5 days, ranging from 5 to 16 days; the children received an average total dosage of 19.3 gm., over an average period of 8.6 days, ranging from 6 to 14 days.   In 5 of the patients (Cases 8, 24, 30, 41, and 44) intravenous antimeningococcic serum was employed in addition to sulfamerazine, with one death (Case 30).   The total amount of serum used in each case was generally small, varying from 30 to 50 cc.   Whether the successfully treated cases in this combined therapy group would have recovered without the additional use of serum cannot be stated definitely.   It is our impression, however, that the drug alone would have achieved the same results.   Fluids were given liberally, usually 2000 to 3000 cc. a day.   None of the patients received alkali therapy.

Determinations of the amount of free drug in the blood were made at frequent intervals in most of the patients.   For those receiving 6 gm. of sulfamerazine per day, plasma concentrations of free drug were as follows in 32 cases: First 12 to 24 hours, 13.4 mg. per 100 cc.; 2d day,

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* These patients were treated on the Medical and Pediatric Wards of the Philadelphia General Hospital (37 cases) and the Hospitals of the University of Pennsylvania (8 cases).

† Sharp & Dohme Laboratories, Glenolden, Pa., kindly supplied the sulfamerazine used in this study.

TABLE I.—ANALYSIS OF DATA ON 45 CASES OF MENINGOCOCCIC MENINGITIS

No.	Age. Yr.	Sex	Duration (days)	Clinical condition on admission	Initial cerebrospinal fluid Turbidity*	Smear	Culture	Blood culture	Sulfamerizine therapy Dur. (days)	Total dose gm.	Toxicity	Course of treatment (days) Clinical improv.	Afebrile	Results and comments
1	36	M	4	Unconscious		+		0	13	81	....			Rec.
2	33	F	2	Stuporous	++++	+	0	0	8	42	....	1	6	Rec.; transient arthritis, onset 8th day
3	41	M	?	Moribund	++	+	0	0	3	20	....	4	4	Died on 3d day
4	51	M	2	Unconscious	++++	+	0	0	11	69	....	2	4	Rec.; transient Bell's palsy, onset 9th day
5	47	M	3	Unconscious	++++	+	+	0	11	63	....	2	6	Rec.
6	22	M	3	Delirious	++	+	+	0	11	63	....	2	6	Rec.
7	46	M	3	Delirious	++++	+	+	0	11	63	....	2	4	Rec.
8	37	M	4	Unconscious	++	+	+	0	14	83	Fever 13th day	4	12	Rec.; barbiturate poisoning, acute alcoholism, 45 cc. antimeningococcic serum, i.v.
9	22	M	2	Drowsy	++++	+	+	0	10	63	....	2	4	Rec.
10	16	F	4	Semiconscious	+++	+	+	0	10	46	Rash 10th day	3	5	Rec.
11	23	M	5	Delirious	++	+	+	0	12	77	Rash 9th day	4	1	Rec.
12	14	M	3	Drowsy	++	+	+	0	8	51		1		Rec.; transient ocular palsy on admission
13	28	F	1	Drowsy	Clear	−	+	0	5	29	Rash 5th day	1	1	Rec.
14	16	M	5	Stuporous	++++	+	+	0	9	47	Fever 8th day	3	4	Rec.
15	42	M	3	Semiconscious	++++	+	+	0	10	81	....	4	5	Rec.
16	23	M	2	Delirious	++++	+	+	+	9	57	....	1	12	Rec.
17	23	F		Unconscious	+++	+	+	0	11	69	....	2		Rec.
18	48	M	3	Drowsy	+++	+	+	0	7	45	....	1	6	Rec.; transient polyarthritis onset 3d day
19	18	F	2	Unconscious	++++	+	+	14		77	Acute loin pain and hematuria 14th day	4	14	Rec.; transient arthritis, onset 8th day
20	50	F	4	Stuporous	++++	+	0	0	16	51	....		5	Rec.
21	17	M	2	Delirious	+++	+	0	0	10	39	....	4	9	Rec.
22	32	M	6	Drowsy	++	+	0	0	10	38	....	2	3	Rec.
23	9	M	1	Stuporous	+++	+	0	0	10	21	....	2	13	Rec.
24	5	M	2	Unconscious	+++	+	+	0	6	15	....	2	3	Rec.; 45 cc. antimeningococcic serum, i.v.
25	3	F	4	Stuporous	++	+	0	0	14	13	....	2	3	Rec.
26	24	M	5	Drowsy	++++	+	0	0	7	45	....	1	3	Rec.
27	11	M	3	Drowsy	+++	+	0	0	7	31				Rec.; transient ocular palsy on admission
28	30	F	5	Delirious	++	+	0	11		69				Rec.; transient polyarthritis on admission
29	29	M	3	Drowsy	++++	+	0	5	33			5	14	Rec.
30	36	M	3	Unconscious	+++	−	+	0	13	105				Died on 21st day, 45 cc. antimeningococcic serum, i.v.
31	7	F	3	Semiconscious	++++	+	0	8	17			1	1	Rec.
32	1	M	3	Drowsy	+++	+	0	9	9					Died 23 hrs. after onset of treatment
33	77	M	?	Unconscious	++++	+	0	8	1			4	11	Rec.
34	28	M	1	Stuporous	++	+	0	7	45			2	4	Rec.
35	43	M	3	Drowsy	+++	+	0	4	27	Fever 7th day				Rec.
36	25	M	2	Semiconscious	++++	+	0	9	25	Rash 9th day	1	6	Rec.
37	25	M	1	Stuporous	++++	+	0	14	83	Rash 14th day	1	2	Rec.
38	2	M	2	Unconscious	++	+	0	8	21	....	3	6	Rec.
39	48	F	6	Stuporous	++	+	0	9	51	Rash 9th day	2	2	Rec.; transient ocular palsy on admission
40	41	F	2	Drowsy	++	+	0	9	56	Fever 8th day	2	6	Rec.
41	16	M	2	Semiconscious	+++	+	0	11	69		3	3	Rec.
42	26	F	2	Semiconscious	++	+	0	6	39		1	9	Rec.; 50 cc. antimeningococcic serum, i.v.
43	13	F	2	Stuporous	+++	+	0	9	54		1	3	Rec.
44	34	F			+++	+	0	9	57		3	6	Rec.; 30 cc. antimeningococcic serum, i.v.
45	5	M	4				0	7	22		2	7	Rec.

* Turbidity: + = less than 1000 cells; ++ = 1000 to 5000 cells; +++ = 5000 to 10,000 cells; ++++ = more than 10,000 cells.
Rec., recovered.

15.7 mg. per 100 cc.; 3d day, 16.5 mg. per 100 cc.; 4th day, 16.0 mg. per 100 cc.; 5th day, 15.5 mg. per 100 cc. Result of blood analyses will be reported in detail later. Lumbar punctures were done on admission for diagnostic purposes, but the procedure was not repeated unless signs of increased intracranial pressure were present or the patient failed to respond to treatment, in which case further study of the cerebrospinal fluid seemed advisable. During the course of this study, however, we did obtain cerebrospinal fluid from 28 patients in order to determine the amount of free drug present. It was found that the mean concentration of the drug in the cerebrospinal fluid was 42.1% of the mean concentration in the plasma.

Results. In this group of 45 patients with meningococcic meningitis treated with sulfamerazine there were 3 deaths (6.7% mortality). Of the fatal cases, one (Case 3) was a 41-year old white man who was moribund on admission and died 3 days later without showing any response to treatment. No history as to the duration of illness was obtainable in this case. The second death (Case 30) was a colored male, aged 36 years, admitted on the 3d day of his disease. At the time of admission the patient was unconscious and had a right-sided torticollis, presumably of cerebral origin. Initial examination of the cerebrospinal fluid revealed marked turbidity, many meningococci on smear, and a positive culture. Subsequent cultures of the fluid on the 5th and 9th days of treatment were sterile. This patient received a total of 105 gm. of sulfamerazine over a period of 13 days and 45 cc. of antimeningococcic serum intravenously on the 3d day. Although the negative cerebrospinal fluid findings were suggestive of some response to the drug, the clinical course was progressively downhill and the patient died on the 21st day. The pertinent autopsy findings were referable to the brain.* There was no gross evidence of meningitis. Areas of recent softening were observed, superimposed on calcification of vessels in the globus pallidum. This lesion was considered to be due to chronic anoxia, to which the meningitis might have been a contributing factor. This could also have accounted for the clinical torticollis and persistent unconsciousness. The third death (Case 33) was a 77 year old white man who was unconscious on admission and died 23 hours after the onset of therapy, having received only 9 gm. of sulfamerazine.

For the successfully treated group, definite clinical improvement, manifested mainly by mental clarity, was apparent within 48 hours of drug therapy in 29 (70%) of the cases, although fever usually persisted for several days following the initial response. The average time observed before the recovered group became afebrile was 5.2 days, ranging from 1 to 14 days. Complications of the disease were observed in 4 patients on admission, 3 with ocular palsies (Cases 12, 27, and 38) and 1 with polyarthritis (Case 28). During the course of treatment, 1 patient (Case 4) developed Bell's palsy, and 3 patients developed

* Examination of the brain was performed by Helena E. Riggs, M.D., Division of Neuropathology, Laboratories, Philadelphia General Hospital.

acute arthritis (Cases 3, 17, and 19). All complications were transient and recovery was complete.

Toxicity. Toxic reactions, attributable to the drug, were noted in 11 patients. Six (Cases 10, 12, 13, 36, 37 and 39) developed skin rashes on the 10th, 9th, 5th, 9th, 14th and 9th days of treatment following 46, 51, 29, 25, 83 and 51 gm. of sulfamerazine respectively. Drug fever was observed in 4 patients (Cases 8, 14, 34 and 40) on the 13th, 8th, 7th and 8th days of treatment after the administration of 77, 41, 45 and 50 gm. of the drug respectively. One patient (Case 19) experienced acute loin pain and gross hematuria on the 14th day of treatment, after having received 77 gm. of sulfamerazine. This case has been reported elsewhere in detail.[2] All of the patients in this sub-group recovered despite the fact that sulfamerazine was discontinued in each instance with the diagnosis of drug toxicity.

Comments. The mortality of 6.7% in this group of 45 cases of meningococcic meningitis treated with sulfamerazine is to be compared with that of 57.5% occurring in 40 cases of this disease observed at the Philadelphia General Hospital during 1935, 1936 and 1937,[7] and with that of 40% in 50 patients reported in 1942.[1] Also the results in this study compare favorably with those recently reported in which sulfadiazine was employed (12.5% mortality).[3] Due to unavoidable circumstances it was not practical to treat any of the cases in this series other than with sulfamerazine.

Toxic reactions due to the drug were more frequent in these patients receiving sulfamerazine than in those previously treated by means of sulfadiazine.[3] However, in a larger group of pneumonia cases in whom sulfamerazine was used over shorter periods of time and in smaller daily doses, the incidence of drug toxicity was negligible.[4]

During the course of this investigation there were 6 additional patients treated with sulfamerazine in whom the diagnosis of meningococcic meningitis was based in each instance on a typical clinical picture, increased spinal fluid pressure, and a turbid cerebrospinal fluid with a high polymorphonuclear cell count. Since the clinical diagnosis in these cases was not substantiated by convincing bacteriologic evidence, we have excluded them from this report, although we believe they represent true cases of the disease. These 6 cases recovered. In addition to the above, there were 3 patients with proven meningococcus meningitis who were moribund on admission and died before sulfamerazine therapy could be instituted.

Summary. 1. Sulfamerazine therapy has been employed in 45 consecutive cases of meningococcic meningitis. There were 3 deaths in the series (6.7% mortality).

2. Definite clinical improvement with return of mental clarity occurred in 70% of the patients within 48 hours. The average time observed for the return to normal temperature was 5.2 days.

3. Toxic reactions attributable to sulfamerazine, occurring in each instance after the 5th day of treatment, were noted in 11 patients.

REFERENCES

1. Campbell, E. P.: Ann. Int. Med., 16, 694, 1942.
2. Clark, J. K., Flippin, H. F., and Murphy, F. D.: Am. J. Med. Sci., 205, 846, 1943.
3. Domm, A. H., Flippin, H. F., Schwartz, L., and Zimmerman, J. J.: New Internat. Clin. (in press).
4. Flippin, H, F., Gefter, W. I., Domm, A. H., and Clark, J. H.: Am. J. Med, Sci., 206, 216, 1943.
5. Goodwin, R. A., Jr., Peterson, O. L., and Finland, M.: Proc. Soc. Exp. Biol. and Med., 51, 262, 1942.
6. Murphy, F. D., Clark, J. K., and Flippin, H. F.: Am. J. Med. Sci., 205, 717, 1943.
7. Riggs, H. E.: Unpublished Report.
8. Roblin, R. O., Jr., Williams, J. H., Winnek, P. S., and English, J. P.: J. Am. Chem. Soc., 62, 2002, 1940.
9. Rose, S. B.: Am. J. Clin. Path., 12, 424, 1942.
10. Sprague, J. M., Kissinger, L. W., and Lincoln, R. M.: J. Am. Chem. Soc., 63, 3028, 1941.
11. Welch, A. D., Mattis, P. A., Latven, A. R., Benson, W. M., and Shiels, E. H.: J. Pharmacol. and Exp. Ther., 77, 357, 1943.

STUDIES ON 2-SULFANILAMIDO-4-METHYL-PYRIMIDINE (SULFAMERAZINE, SULFAMETHYLDIAZINE) IN MAN

IV. THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA*

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In the preceding article we reviewed the therapeutic effectiveness of sulfamerazine (2-sulfanilamido-4-methyl-pyrimidine, sulfamethyldiazine) against experimental infection, discussed the behavior of the drug in man, and presented observations on its use in the treatment of meningococcic meningitis. The present paper deals primarily with the treatment of pneumococcic pneumonia with sulfamerazine.†

Organization of the Study. A prime requirement in the evaluation of a new chemotherapeutic agent for the treatment of pneumonia is to compare it with a proven form of therapy. Therefore, from the beginning of this study (January 1, 1943), as in previous studies of sulfonamide therapy in pneumonia, the medical services‡ in the hospital were divided into two therapeutic groups, one receiving sulfamerazine, and a control group, consisting of an equal number

* From the Philadelphia General Hospital Committee for the Study of Pneumonia, which also includes J. G. Reinhold, Ph.D., and S. B. Rose, M.D.
† Sharp & Dohme Laboratories, Glenolden, Pa., kindly supplied the sulfamerazine used in this study.
‡ Clinical facilities were given us for this study by the following Chiefs of Service: Drs. Frieda Baumann, R. S. Boles, C. L. Brown, Thomas Klein, D. W. Kramer, D. N. Kremer, W. G. Leaman, Jr., S. A. Loewenberg, and T. G. Schnabel.

of patients with pneumonia, receiving sulfadiazine. For this report we have taken the first 80 cases in each therapeutic group. In general, the distribution of age and sex (Table 1), and the day of disease on which treatment was begun (Table 2) were comparable in the two groups.

TABLE 1.—MORTALITY ACCORDING TO AGE AND SEX GROUPS

Age group (yrs.)	Sulfamerazine treated		Sulfadiazine treated	
	No.	Died	No.	Died
12–19	10	..	8	
20–29	11	..	14	
30–39	23	1	15	1
40–49	16	2	21	2
50–59	10	2	14	4
60 and over	10	1	8	1
Sex				
Male	70	5	73	8
Females	10	1	7	

TABLE 2.—MORTALITY IN RELATION TO DAY OF DISEASE ON WHICH TREATMENT WAS BEGUN

Day of disease treatment started	Sulfamerazine treated		Sulfadiazine treated	
	No.	Died	No.	Died
1	8 ⎫	1	6 ⎫	
2	16 ⎬ 67.5	1	15 ⎬ 55.0	
3	15 ⎭	..	10 ⎭	2
4	15 ⎫	..	13 ⎫	
5	11	1	10	1
6	7 ⎬ 32.5	..	9 ⎬ 45 0	
7	5	2	10	1
7+	3 ⎭	1	7 ⎭	4

The diagnosis of typical pneumonia was established in every case by the natural history of the disease and the findings on physical examination. When indicated, the diagnosis was confirmed by roentgen studies. Pneumococci were isolated from the sputum or blood stream of 134 patients (70 sulfamerazine, 64 sulfadiazine). A specific type of pneumococcus was recovered from 73 of the cases (35 sulfamerazine, 41 sulfadiazine). A higher incidence of typed pneumococci would undoubtedly have been obtained had we employed typing as a routine procedure. Instead, typing was done on those pneumococci isolated from the blood stream and those found in the sputum samples of seriously ill patients. In 26 cases (10 sulfamerazine, 16 sulfadiazine) we were unable to confirm the clinical diagnosis of a pneumococcic infection by convincing bacteriologic studies because sputum samples were either unobtainable or else failed to yield pneumococci on stained smear and culture of the sputum. Repeated blood counts, urinalyses, blood cultures, and determinations of free and total drug in the blood plasma were made in all patients receiving sulfamerazine or sulfadiazine. Other laboratory studies were carried out as indicated.

Dosage. With sulfamerazine, two dosage schedules were employed: an initial 3 gm. dose by mouth was followed by 1 gm. every 6 hours in the first 23 patients treated; the remaining 57 patients received the 1 gm. dose every 8 hours. With sulfadiazine, the dose schedule was the same as that used with sulfamerazine, except that all of the patients in this group were given 1 gm. every 6 hours. The average total dosage for the successfully treated patients receiving sulfamerazine was 24.4 gm. (4 gm. daily for 5.6 days), or 22.7 gm. (3 gm. daily for 6.5 days), as compared with 30.8 gm. for the sulfadiazine treated group (4 gm. daily for 7 days). In certain instances, when a rapid elevation of the blood level of either drug was desired, the initial 3 gm. of drug was given by vein. A 5% solution of the sodium salt of sulfamerazine or sulfadiazine in sterile distilled water was employed in such cases. When sulfa-

merazine or sulfadiazine failed to bring about a favorable clinical response within 36 to 48 hours, the patient was usually given specific serum. Of the 160 patients included in this report, 12 (6 sulfamerazine, 6 sulfadiazine) received serum together with chemotherapy. In addition, a single case in each therapeutic group was given penicillin. All patients received at least 2500 cc. of fluid during each 24-hour period, and those treated with sulfadiazine were given either sodium bicarbonate or sodium citrate[8] in an amount equal to that of the drug.

Therapeutic Results. The results of treatment in the 2 therapeutic groups are shown in Table 3. Of the patients treated with sulfamerazine, 6 died, and in the sulfadiazine treated group, 8 died, the mortality rates being 7.5% and 10%, respectively. Eighteen patients with bacteremia were treated with sulfamerazine and 6 of these died (33.3% mortality). In the sulfadiazine treated group, 4 of the 22 bacteremic patients died (18.2% mortality). The fatal cases are analyzed in Table 4.

TABLE 3.—DISTRIBUTION OF TYPES, BACTEREMIA, AND MORTALITY RATES

	Sulfamerazine treated				Sulfadiazine treated			
	All cases		Bacteremic cases		All cases		Bacteremic cases	
Type	No.	Died	No.	Died	No.	Died	No.	Died
I	6	..	3	..	10	2	4	1
II	3	1	1	1	6	..	4	
III	3	1	2	1	2	..	1	
Group IV . . .	21	4	12	4	24	3	13	3
Others	47	..	..	..	38	3		
Total	80	6	18	6	80	8	22	4
Mortality % . .	7.5		33 3		10 0		18 2	

In evaluating any therapeutic agent clinically, one must consider the effect of the agent on the course of the disease,as well as its influence on the mortality incidence. As shown in Table 5, a critical drop in temperature occurred within 24 hours in 51.4% of the patients treated with sulfamerazine, as compared with 30.6% of the patients in the sulfadiazine treated group. Within 48 hours, 77.1% of the patients receiving sulfamerazine and 66.7% of those treated with sulfadiazine showed a critical drop in temperature. The temperature returned to normal within 24 hours in 17.5% of the patients in the sulfamerazine treated group and in 15.3% of the patients receiving sulfadiazine. Within 72 hours a return to normal temperature occurred in 72.9% and 59.8% of patients in the sulfamerazine and sulfadiazine groups respectively.

Complications. The incidence of complications was low (7 cases, 4.4%) for the entire series of 160 patients (Table 6), 2 (2.5%) occurring in the sulfamerazine and 5 (6.3%) in the sulfadiazine treated group. Three cases (1 sulfamerazine, 2 sulfadiazine) developed endocarditis; all of these patients died. Empyema occurred in 3 sulfadiazine treated cases with no deaths. A single patient receiving sulfamerazine developed meningitis and failed to recover. In this sub-group all patients with the exception of the case with meningitis were started on drug therapy after the 6th day of the disease.

TABLE 4.—ANALYSIS OF FATAL CASES

No.	Age (yrs.)	Day of disease treatment begun	Type	Blood culture	No. of lobes involved	Total drug (gm.)	Total serum (units)	Remarks
					Sulfamerazine			
1	46	1	XXV	Pos.	3	56	200,000	No response to treatment; aut.: lobar pneumonia of entire right lung
2	61	5	XVI	Pos.	2	22		Cardiac failure on adm.; no autopsy
3	41	2	II	Pos.	2	33	100,000	Rt. phthisis bulbæ, pansinusitis on adm.; purulent ophthalmitis 4th day; convulsions on 13th day; aut.: resolving lobar pneumonia, meningitis, purulent sphenoiditis
4	33	7	VIII	Pos.	5	15	100,000	Chr. alcoholism; no response to treatment; aut.: lobar pneumonia of all 5 lobes
5	51	28	XII	Pos.	3	36	100,000	Clin. picture of ac. bact. endocarditis; serum sensitive; received penicillin 250,000 units; no aut.
6	58	7	III	Pos.	3	8	100,000	Moribund on adm. with leukopenia; aut.: lobar pneumonia of both lower lobes.
					Sulfadiazine			
1	50	10	VII	Pos.	2	19		Responded well to treatment; developed ac. pulm. edema, sudden death; no aut.
2	51	4		Neg.	1	8		Moribund on adm.; no response to treatment; died in 36 hrs.; aut.: lobar pneum.
3	44	7	I	Neg.	4	7	100,000	Moribund on adm.; no response to treatment; died in 30 hrs.; aut.: lobar pneum. of entire right lung and left lower lobe
4	68	20		Neg.	2	27		Responded well to treatment; drug stopped on 6th day; died on 9th day, cardiac decomp.; no autopsy
5	54	5	XI	Pos.	4	11		Moribund on adm.; no response to treatment; aut.: lobar pneumonia involving 4 lobes
6	53	21	XXIV	Pos.	3	23	120,000	No response to treatment; penicillin 160,000 units; aut.: resolving lobar pneum., ac. bact. endocarditis
7	34	4			1	22		Ac. pulm. edema on adm.; on response to treatment; aut.: lobar pneumonia
8	45	10	I	Pos.	3	51		Diabetes mellitus; initial response to treatment, then relapse; aut.: resolving lobar pneumonia, ac. bact. endocarditis

TABLE 5.—EFFECT OF TREATMENT ON TEMPERATURE RESPONSE (146 CASES)*

	Sulfamerazine treated		Sulfadiazine treated	
	No.	%	No.	%
Critical fall in temperature:				
Within 24 hours	38	51.4 ⎫	22	30.6 ⎫
Within 48 hours	19	25.7 ⎬ 77.1	26	36.1 ⎬ 66.7
Over 48 hours	17	22.9 ⎭	24	33.3 ⎭
Temperature at normal level:				
Within 24 hours	13	17.5 ⎫	11	15.3 ⎫
Within 48 hours	28	37.9 ⎬ 72.9	20	27.8 ⎬ 59.8
Within 72 hours	13	17.5 ⎭	12	16.7 ⎭
Over 72 hours	20	27.1	29	40.2

* All deaths excluded.

TABLE 6.—INCIDENCE OF COMPLICATIONS AND TOXIC REACTIONS (160 CASES)

	Sulfamerazine treated		Sulfadiazine treated	
Complications	No.	%	No.	%
Endocarditis	1	1.3	2	2.5
Empyema	..	..	3	3.8
Meningitis	1	1.3		
Total	2	2.5	5	6.3
Toxic reactions				
Vomiting	2	2.5	2	2.5
Hematuria (micro.)	3	3.8	4	5.0
Psychosis	1	1.3		
Drug fever	1	1.3	2	2.5
Total	7	8.9	8	10.0

Toxic Reactions. In this series of 160 patients the incidence of toxic reactions attributable to either drug was small (9.4%) and comparable for the two therapeutic groups (Table 6). Vomiting was noted in 2 patients in each group, but in no patient was it necessary to stop drug therapy since the symptom was transient. Microscopic hematuria was encountered in 3 patients receiving sulfamerazine and in 4 patients treated with sulfadiazine. Crystalluria was detected in approximately 15% of each group. No cases of gross hematuria, anuria, or renal pain were observed with either drug. The diagnosis of a drug psychosis was made in a single patient who was treated with sulfamerazine. Drug fever developed in 3 patients (1 sulfamerazine, 2 sulfadiazine). Repeated blood studies showed little evidence of a marked reduction in hemoglobin, red blood cell, or white blood cell counts that could be attributed to either drug.* No skin rashes were observed.

Blood Concentration of Sulfamerazine and Sulfadiazine.[7] The average concentration of free sulfamerazine in plasma as shown by daily determinations during the entire period of treatment was 12.7 mg. per 100 cc. (4 gm. daily), and 10.9 mg. per 100 cc. (3 gm. daily), compared with an average concentration of free sulfadiazine in plasma of 7.9 mg. per 100 cc. (4 gm. daily).

Comment. Sulfamerazine and sulfadiazine are both effective drugs in the treatment of pneumococcic pneumonia. The mortality of 7.5% in the sulfamerazine group and 10% in the sulfadiazine group compare favorably when all of the factors influencing fatality are considered.[3] Clinical response, as manifested by a fall in temperature, was slightly more in evidence with sulfamerazine than with sulfadiazine; and this, we believe, may be related to the more rapid rise and higher concentrations in blood attained by sulfamerazine as compared with sulfadiazine.[5,6]

In both therapeutic groups there was a low incidence of toxic manifestations (none of which was serious) following the use of these drugs. It is to be remembered, however, that the hazard of severe toxic reactions increases with the prolonged use of both sulfamerazine[1,4] and sulfadiazine.[2] In this series of pneumonia cases most patients required no more than 20 to 30 gm. of either drug, extending over a period of approximately 6 days. We believe that this explains in part the low incidence of toxicity encountered in this study.

Summary. 1. Sulfamerazine was given to 80 adult patients with pneumococcic pneumonia and the response was compared with that of a control series of 80 adult patients treated with sulfadiazine.

2. Mortality in the two therapeutic groups showed no significant difference (sulfamerazine 7.5%, sulfadiazine 10%).

3. Sulfamerazine tended to lower the temperature somewhat more rapidly than did sulfadiazine; however, the duration of chemotherapy and the incidence of complications were essentially the same for the two groups.

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* Dr. Walter J. Crocker, Chief of the Division of Clinical Pathology of the Laboratories of the Philadelphia General Hospital, coöperated with the authors in this phase of the work.

4. The incidence of toxic reactions was low and comparable for both sulfamerazine and sulfadiazine. No serious reactions were encountered with either drug.

5. The group treated with sulfamerazine showed higher plasma concentration of free drug than did the group receiving larger or equivalent amounts of sulfadiazine.

REFERENCES

1. Clark, J. K., Flippin, H. F., and Murphy, F. D.: Am. J. Med. Sci., 205, 846, 1943.
2. Flippin, H. F.: Med. Clin. North America, p. 1799, November, 1941.
3. Flippin, H. F., Schwartz, L., and Clark, J. H.: Ann. Int. Med., 14, 1969, 1941.
4. Gefter, W. I., Rose, S. B., Domm, A. H., and Flippin, H. F.: Am. J. Med. Sci., 206, 211, 1943.
5. Goodwin, R. A., Jr., Peterson, O. L., and Finland, M.: Proc. Soc. Exp. Biol. and Med., 51, 262, 1942.
6. Murphy, F. D., Clark, J. K., and Flippin, H. F.: Am. J. Med. Sci., 205, 717, 1943.
7. Reinhold et al.: To be published in detail.
8. Schwartz, L., Flippin, H. F., Reinhold, J. G., and Domm, A. H.: J. Am. Med. Assn., 117, 514, 1941.

TISSUE CULTURE STUDIES ON CYTOTOXICITY OF BACTERICIDAL AGENTS

III. Cytotoxic and Antibacterial Activity of Gramicidin and Penicillin; Comparison with Other Germicides

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In the first paper of this series[6] a report was made of the relative toxicity of certain bactericidal agents as determined by their influence on the extent of migration of lymphocytes in tissue culture preparations. We reported also on the antibacterial activity of these agents on Gram-positive cocci growing in a tissue culture medium similar to that used in the toxicity tests.[4,5] It was of interest to compare the bactericidal agents of microbial origin with other antiseptics by the use of these methods. Many germicides known to be useful for sterilization of the skin or other surfaces are not effective against bacteria in the presence of serum and tissue extract. Likewise, many germicides are quite toxic for tissue cells although they may be used safely on the skin. As a result, the choice of germicides that might be compared with gramicidin and penicillin under these conditions was limited. Merthiolate was included because it prevented the growth of bacteria under the conditions of the test, even though it is known that the tissue toxicity of the mercurial compounds as a class is rather high. One

member of the sulfonamide group of drugs was tested although it was assumed that the inhibitors present in the tissue culture medium would affect its activity greatly. The other two germicides studied were zephiran* and phemerol,* two synthetic detergents, both of them being cationic, quaternary ammonium compounds.

The results of cytotoxicity tests with penicillin were taken from the first paper of this series.[6] These tests were not repeated because they required the use of rather large amounts of penicillin. The same sample of penicillin was used in these tests and in the bactericidal tests reported in the present study.

Experimental. The method of determining the toxicity of each test substance has been described elsewhere.[5] Tissue was taken under sterile conditions from the mesenteric lymph node of the rabbit. Explants approximately 1.5 mm. across were carefully matched for size and shape and were divided into three similar groups each containing 12 fragments. One group of fragments was used in the control series of cultures and the second and third groups were used in the test series. One test was made with each of several different concentrations of each germicide. It was convenient to test only two dilutions of the same germicide or a single dilution of each of two germicides in the same experiment.

The penicillin used in these experiments had a potency of 35 Oxford units per mg. Solutions of penicillin in Tyrode's solution were prepared and stored in solid carbon dioxide. Stock solutions and suspensions of gramicidin were prepared as previously described. Dilutions of merthiolate, zephiran and phemerol were made from the commercial preparations containing 0.1% of each drug in aqueous solutions. Solutions containing sodium sulfathiazole were made in Tyrode's solution. Solutions containing germicides were brought · to pH 7.6 just before the material was added to the culture medium.

Each culture was planted on a 22 mm. round coverslip and consisted of an explant of lymph node placed in the center of a clot consisting of 1 drop of heparinized rabbit's plasma and 3 drops of a rabbit's serum extract of chick embryos. An appropriate dilution of the germicide to be tested was added to the tissue extract at the time the culture was made in an amount equal to a tenth of the volume of the final tissue culture clot. A similar solution not containing the drug (Tyrode's solution, sterile distilled water or, in the case of gramicidin, Tyrode's solution containing ethyl alcohol) was added to cultures of the control series. Cultures were incubated as lying drops at 37° C. for 24 hours. At the end of the period of incubation the extent of migration of lymphocytes was determined by the use of an ocular micrometer at a magnification × 60. The distance from the edge of the original explant to the outer limit of migrating cells was measured at the widest part of the migration zone. The mean migration was determined for each group of 12 fragments and the values obtained for the test series were compared with those of the control series and were expressed in terms of percentage of inhibition.

The same kind of tissue culture medium was used in the bactericidal tests. Three strains of Gram-positive cocci were employed because they represent species of bacteria commonly found in local pyogenic infections. The strain of D. pneumoniæ Type VII was obtained from material removed from an empyema cavity and the strains of S. aureus and S. pyogenes were obtained from the blood of patients suffering from bacteremia. The strains of D. pneumoniæ Type VII and S. pyogenes were grown on Hartley's horse muscle digest broth containing 10% of horse serum. The strain of S. aureus was maintained on Hartley's broth alone. Dilutions of the bacterial cultures were made in

*Zephiran is the trade name for alkyl dimethyl benzyl ammonium chloride (alkyl = C₈ to C₁₈), Alba Pharmaceutical Company. Phemerol is para-tertiary-octyl-phenoxy-ethoxy-ethyl-dimethyl-benzyl ammonium chloride monohydrate, Parke, Davis & Company.

Hartley's broth and added to the tissue extract in the proportion of 1 part of a suspension of bacteria in broth to 40 parts of tissue extract. A sufficient amount of the original culture was used to cause the appearance of 20 or more bacterial colonies in each of the control cultures.

Dilutions of the germicide in Tyrode's solution were added to both the heparinized rabbit's plasma and tissue extract at the time the cultures were made. One part of solution containing germicide was added to 9 parts of plasma or tissue extract. Similar amounts of a corresponding solution not containing germicide were added to control cultures. Each culture consisted of 1 drop of plasma and 3 drops of tissue extract placed on a 22 mm. round coverslip. Four cultures were prepared for each experimental condition. Cultures were incubated at 37° C. for 48 hours. At this time the presence of bacterial colonies was determined by examination with a dissection microscope at ×7 magnification. The least amount of germicide that would completely prevent the appearance of bacterial colonies in all four cultures after incubation for 48 hours was determined for each bacterial strain tested. Two independent determinations of the end-point were made for each germicide.

Results. The results obtained in the tests on cytotoxicity are presented in Figure 1. Although considerable variation may exist in the determination of the percentage of inhibition taking place for any particular amount of germicide used, the general relationship between these drugs is fairly represented in the figure. Merthiolate is seen to be the most toxic. The use of 60 μg. per cc. of the drug produced a 72% inhibition of the migration of lymphocytes in 24 hours. Zephiran and phemerol were next in order of toxicity. The use of 100 μg. per cc. of gramicidin produced but a 24% inhibition. Penicillin and sodium sulfathiazole were the least toxic, it being necessary to use several hundred μg. per cc. of each before any effect was noted.

TABLE 1.—AMOUNT OF GERMICIDE (MICROGRAMS PER CC.) CAUSING INHIBITION OF BACTERIA

Germicide	Organism*		
	D. pneumoniæ Type VII	S. aureus	S. pyogenes
Penicillin	3.0	5	5
Gramicidin	0.6	100	10
Merthiolate	25.0	50	50
Zephiran	25.0	20	8
Phemerol	25.0	16	10
Sodium sulfathiazole	1000	Inhibition†	Inhibition†

* Two experiments were carried out for each germicide on each organism.
† Not complete with 2500.

The results of bactericidal tests are presented in Table 1. Penicillin was very effective against all three bacterial strains. Small amounts of gramicidin prevented the growth of pneumococci and hemolytic streptococci but comparatively large amounts were necessary to prevent the growth of staphylococci. Gramicidin has been found to be even less inhibitory for five other strains of S. aureus that we have tested. On the other hand, zephiran and phemerol were quite effective against S. aureus as well as against the other two test organisms. Merthiolate was as active as the two detergents in preventing the growth of pneumococci but larger amounts were needed to inhibit staphylococci and hemolytic streptococci. Sodium sulfathiazole was relatively ineffective against S. aureus and S. pyogenes and it was

necessary to use 0.1% of this drug to prevent the growth of pneumococci.

Under these conditions penicillin again was found to be superior to other germicides because of its bactericidal activity against Grampositive cocci and its low toxicity for tissues. The cytotoxicity of the two detergents tested was not very much greater than that of gramicidin and their bactericidal activity compares favorably with that of gramicidin.
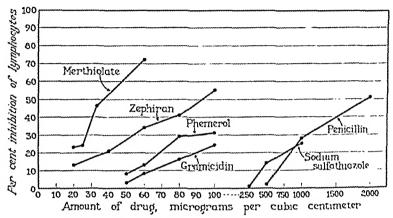
FIG. 1.—Cytotoxicity of various concentrations of bactericidal agents.
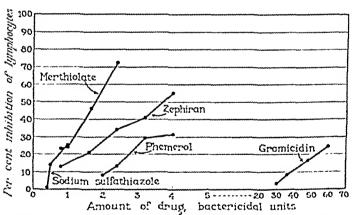
FIG. 2.—Cytotoxicity of germicides in concentrations expressed in multiples of the given drug necessary to inhibit D. pneumoniæ.

Figures 2, 3 and 4 represent the result of the combination of data given in Table 1 and Figure 1. Figure 2 represents the order of cytotoxicity of the germicides studied, with the exception of penicillin, in terms of the amount of drug necessary to inhibit pneumococci. The amount of drug used in each cytotoxicity test is expressed as the ratio of the actual amount of drug used in the test to the amount bactericidal for D. pneumoniæ. Thus, if the amount used in a toxicity test was

80 µg. per cc. and 20 µg. per cc. of the germicide was bactericidal for the strain of pneumococcus used, then the value was expressed as 4 bactericidal units in Figure 2. Figure 3 presents the toxicity of the germicides studied in relation to the amount of each one necessary to inhibit *S. aureus*, and Figure 4 is a similar representation in relation to the amount of each agent necessary to inhibit *S. pyogenes*. The toxicity of penicillin was so low compared with its bactericidal activity that the values obtained could not be included conveniently in Figures 2, 3 and 4.
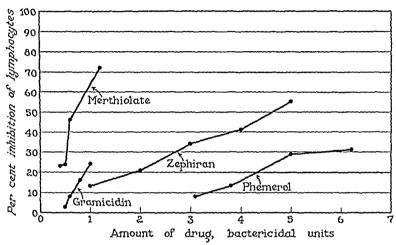
Fig. 3.—Cytotoxicity of germicides in concentrations expressed in multiples of the amount of the given drug necessary to inhibit *S. aureus*.
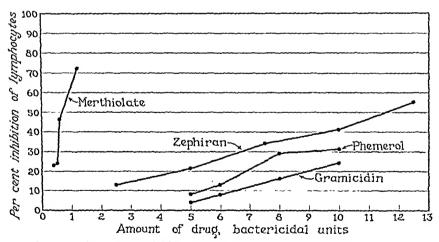
Fig. 4.—Cytotoxicity of germicides in concentrations expressed in multiples of the amount of the given drug necessary to inhibit *S. pyogenes*.

Baker, Harrison and Miller[1] have shown that the cationic detergents are frequently more bactericidal than the anionic detergents and that they are effective against Gram-positive and Gram-negative species. Zephiran and phemerol are cationic detergents and are effective in

small amounts against the Gram-positive cocci tested. They, like some other detergents, are hemolytic in small concentrations in the presence of serum and therefore could not be used with safety by the intravenous route.

We have previously pointed out[3] some of the biologic similarities between gramicidin and the anionic detergents. Baker, Harrison and Miller[2] have shown that the ability of gramicidin to decrease the respiration of bacteria is inhibited by the addition of demal, a unionized detergent capable of inhibiting the activity of anionic and cationic detergents alike. In accord with this observation, we have found that a bactericidal amount of gramicidin is rendered ineffective against pneumococci growing in the tissue culture clot if it is first mixed with a bactericidal amount of the cationic detergent, phemerol.[4] Bacteriostasis results only when an excess of either phemerol or gramicidin is present. These findings contraindicate the simultaneous use of gramicidin and a cationic detergent but do not necessarily contraindicate the use of gramicidin in the presence of the anionic synthetic detergents or any of the ordinary soaps. The antibacterial activity of penicillin was not inhibited by either gramicidin or the two cationic detergents, phemerol or zephiran.

Conclusions. A comparison has been made of the bactericidal and cytotoxic activity of gramicidin, penicillin and a few of the commonly used antiseptics. For the three organisms tested, namely, one strain each of *D. pneumoniæ*, *S. aureus* and *S. pyogenes*, penicillin was superior in germicidal properties to the other agents.

While gramicidin is effective in small amounts against *D. pneumoniæ* and *S. pyogenes*, it is relatively ineffective against *S. aureus*. On the other hand, zephiran and phemerol are quite effective against *S. aureus* as well as against the other two test organisms. Furthermore, penicillin is superior to the other germicides tested because of its low toxicity for tissues. Gramicidin produces less toxicity for tissue than the other germicides studied with the exception of penicillin. Of the other germicides, the two detergents, phemerol and zephiran, compare quite favorably with gramicidin in regard to their cytotoxicity.

The antibacterial activity of gramicidin, which behaves like an anionic detergent, can be neutralized by a cationic detergent, phemerol. The simultaneous use of gramicidin and a cationic detergent in the treatment of infections is, therefore, contraindicated. There is no contraindication to the simultaneous use of gramicidin with penicillin or the anionic detergents including the ordinary soaps.

REFERENCES

1. BAKER, Z., HARRISON, R. W., and MILLER, B. F.: J. Exp. Med., 73, 249, 1941.
2. BAKER, Z., HARRISON, R. W., and MILLER, B. F.: J. Exp. Med., 74, 621, 1941.
3. HEILMAN, D., and HERRELL, W. E.: Proc. Soc. Exp. Biol. and Med., 47, 480, 1941.
4. HEILMAN, D., and HERRELL, W. E.: Proc. Staff Meet., Mayo Clin., 17, 321, 1942.
5. HERRELL, W. E., and HEILMAN, D.: J. Clin. Invest., 20, 583, 1941.
6. HERRELL, W. E., and HEILMAN, D.: Am. J. Med. Sci., 205, 157, 1943.

PROTRUDED INTERVERTEBRAL DISK AND HYPERTROPHIED LIGAMENTUM FLAVUM. CRITERIA FOR DIAGNOSIS AND INDICATIONS FOR OPERATION

WITH ANALYSIS OF 50 SURGICALLY TREATED CASES*

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THE concepts regarding the mechanism and management of low-back pain and the so-called sciaticas have in the past several decades reflected the advances of accurate knowledge as well as fads in medical practice. The gynecologic surgeon at one time sacrificed many normal organs in a futile attempt to relieve these symptoms. Suspension of viscera, especially the kidney, had its flare. Then followed the universally accepted concepts of sacro-iliac and lumbosacral sprains, the myositis of the Scandinavians, the fibrositis and fasciitis of the British and the focal infections of the Americans. All these concepts served some purpose and most of the patients apparently improved or recovered even though scientific proof of the validity of the concepts was frequently missing. In more recent years the deficiency states have received their share of attention and in the last 2 or 3 years the protruded intervertebral disk has become most prominent.

The clinicians for years have sought anatomic explanations for the puzzling problem of the low-back pain and sciatica. Carnett and Bates[2] long championed the concept of intercostal neuralgia, feeling that the nerve irritation was mechanical in nature and in the proximity of the intervertebral foraminæ. Feiling,[6] based on his studies of a large number of cases, felt that many of the so-called sciaticas are really forms of radiculitis. With a better knowledge of the specific inflammatory lesions of the roots as in tabes dorsalis, and in compressive lesions as in extramedullary spinal cord conditions, a better understanding of root irritation was obtained. It is therefore surprising that lesions of the intervertebral disks should have received so little attention until recent years.

The intervertebral disks make up about one-quarter of the entire length of the vertebral column and in the lumbar region are relatively larger, constituting about one-third of that part of the spinal column. Considering the anatomic makeup of the disks and the rôle they play in movements of the lower spine, it is not surprising that they are often the seat of disease or injury. Although attention was called to disease and injury of the disks as far back as 1896[7] and although cases of protrusion have been described as chondromas by many authors,[9] it was not until 1934 that Mixter and Barr[9] established the protrusion of the

disk as a definite clinical entity. Since then it has become progressively more popular, reaching the point where some neurosurgeons[3] regard sciaticas and recurrent low-back pain as being almost universally due to a protruded disk.

Based on our experience we feel that the recognition of the protruded disk is an important practical addition in the management of the troublesome low-back pain and sciaticas. However, we feel that it is by no means the only important cause of this syndrome and that there is definite need for conservatism in diagnosis and management. It is with this in mind that we are reviewing 50 verified cases, each of which was personally studied by one of the authors and many by both. An attempt will be made to establish some criteria for diagnosis and treatment, and more particularly point out some pitfalls in the management of these cases. No attempt is made to review the literature, since this has been magnificently covered by Bradford and Spurling.[1]

Anatomy. The *gross* pathologic changes as observed at operation consist of one or more of the following:

1. Lateral protrusion of the nucleus pulposus with or without rupture of the annulus fibrosus are the most constant findings. The rather strong firmly attached posterior longitudinal ligament favors the lateral rather than the median protrusion. The protrusion is usually unilateral but may be bilateral. The lateral protrusion causes pressure on the spinal roots and explains the so-called "sciatic" pain.

The gross appearance of the excised disk depends on whether or not it was removed *en masse* or in several fragments. Removed in one piece, it measures from 0.5 to several centimeters and appears to consist of fibrous tissue which makes it look like wet, rolled up blotting paper. In addition there are often small, soft, pointed processes with a shiny surface. When it is removed in fragments, the appearance is less striking. The excised material is grayish white and, while usually soft, may be quite firm.

2. The lateral herniations are often productive of adhesions if they have ruptured through the annulus fibrosus. These adhesions may occur between the nucleus and root, or between the root and the ligamentum flavum. The density of the adhesions increases with the longevity and severity of the symptoms. In a few cases where the root sheaths were opened, dense adhesions were found within, matting together the fibrils and these in turn to the meninges. This may explain the residual symptoms in some of the cases.

3. Small herniations in the midline without rupture of the annulus fibrosus with little or no root compression were encountered in some cases. These cases were associated with considerable backache and but little pain in the lower limbs.

4. Hypertrophy of the ligamentum flavum associated with a herniated nucleus pulposus is an almost constant finding. The only cases where it was conspicuously not hypertrophied were the acute cases. The hypertrophy of the yellow ligament seemed to bear a relationship in degree to the length and severity of the symptoms, particularly those involving the back and its musculature.

5. Varices of the meningo-rachidian veins and of the root sheaths were found in a number of cases.

The *microscopic* changes in the protruded disk have been described by Deucher and Love.[4] In most cases there were microscopic changes in both the annulus fibrosus and nucleus pulposus. Fissures in the annular and nuclear parts were a constant finding. In the 100 cases studied, 32 showed degenerative changes, 28 fibrosis, and 22 edema.

The microscopic changes in the hypertrophied ligamentum flavum were described by Dockerty and Love,[5] and by Lewy and Groff.[8] The principal changes include splitting, fraying and fibrillation of the normal elastic fibers, varying degrees of fibrosis, hyaline changes in blood-vessels and occasional calcification.

Analysis of Surgically Treated Cases. The authors have observed many more than 50 cases, but 50 were selected because they were carefully studied and observed between 1938 and 1942 by at least one of us. A number of verified recent cases were not included by reason of lack of knowledge of end-results. With one exception, all these patients were operated on at Graduate Hospital, most of them by Dr. F. C. Grant and Dr. R. A. Groff, and a few by Dr. E. O. Jeffreys. One case was studied in Philadelphia and operated on by Dr. S. N. Rowe in Pittsburgh.

The more important findings are summarized in Table 1. These will now be briefly discussed.

Sex and Age Incidence. The condition is considerably more common in the male than in the female. It may occur at any age but the average age is 39.6 years.

TABLE 1.—ANALYSIS OF DATA

Sex	M, 31; F, 19
Age	23–64 (average, 39.5)
Trauma	28 (severe, 7; slight, 21; none, 22)
Duration of symptoms	Short, 3 mos.; long, 29 yrs.; average, 4.3 yrs.
Intermissions	Occurred, 32 cases; absent, 18 cases
Aggravating factors	Bending, 42; coughing and sneezing, 41; lifting, 37; walking, 35; sitting, 29; lying, 25
Location of symptoms:	
Initial	Backache, 41; pain in limbs, 9
Prior to operation	Back, 47; L. lower limbs, 29; R. lower limbs, 20
Degree of disability	Major, 42; moderate, 7; slight, 1

History of Trauma. In more than half of the cases there is a history of some trauma, as a rule slight. Lifting, falling and twisting of the trunk are the most commonly recorded modes of injury. There were relatively few major traumas of the vertebral column, which could be regarded as antecedent factors for the protruded disk.

Duration of Symptoms—Frequency of Intermissions. The average duration symptoms was 4.3 years. Intermissions were observed in 32 cases (varying from days to many years). A careful history in some severe cases would elicit that during the so-called free interval the patient was extremely careful not to "strain" the back. In some cases severe attacks were precipitated by mere bending or light lifting. On the other hand, some patients did hard work for years without any ill-effects.

Location of Symptoms. The *initial* symptom in the majority of cases was located in the back, usually in the middle and paravertebral portions of the back. Rarely was it unilateral and only in 9 cases did it radiate down one limb. Later in the course of the process backache still remained a prominent feature; but pain in the legs occurred in 49 of the cases, usually being unilateral.

Character of Pain and Aggravating Factors. The pain is usually deep, unaccompanied by nerve or superficial tenderness, and always aggravated by one or more of the several factors such as bending, sneezing and coughing, lifting, etc. One has the impression after examining these patients that unlike spinal cord tumors or inflammatory lesions the pain is mechanical in nature.

Degree of Disability. Of the 50 cases, 42 had a major disability, *i. e.*, were unable to pursue their work and required sedatives and some narcotics. Those moderately disabled could get along but had some pain, especially backache.

It should again be noted that backache is nearly a constant symptom in displaced disk, but unless it becomes severe the patient does not regard it as a real disability.

Objective Abnormalities. Though each patient received a detailed somatic and neurologic examination, only the more frequently encountered abnormalities are recorded here. Fortunately, these observations require but a few minutes to elicit. An inspection of the back and of the two pelvic crests followed by palpation and testing the mobility of the spine gives most valuable information. The following findings were noted: diminished lordotic curve, 47; tilting of pelvis, 36; muscle spasm, 48; alteration of knee reflexes, 9; alteration of Achilles reflexes, 21; hypesthesia, 4; Lasègue sign positive, 42 (bilateral, 22; unilateral, 20).

Each of these signs are, of course found in conditions other than the protruded disk. However, the occurrence of most of them in the same patient plus the suggestive historical data, and the exclusion of other disease makes these findings extremely important in diagnosis.

It should be stressed that the Lasègue test behaves rather peculiarly in some of these conditions, in that testing the contralateral leg gives rise to the inability to extend the tested leg, but pain in the opposite side.

Again it is worth stressing that sciatic nerve tenderness, so frequently observed in neuritis, was rarely seen in this series.

In addition, there were neurologic abnormalities of relative infrequency: There was 1 case of atrophy of the thigh and there were 3 with weakness and atrophy of one foot. One case had definite sphincter disturbances.

We learned in routine testing that normally the muscles of the *left* big toe, especially the extensors, are definitely weaker than those of the right big toe.

During the last 2 years we have used some of the newer tests which may prove of some value. One of these consists in flexing the chin upon the sternum, and the other in compressing the jugular vein.[14, 15] Both of these tests proved of no more than confirmatory value.

Contrast Medium Studies. In the beginning only lipiodol was used as a contrast medium. More recently only air has been used. With few rare exceptions the air myelogram is a reliable diagnostic procedure. Air studies are unsatisfactory in the examination of lesions between L–V and S–1 and often in the cervical swelling of the spinal cord. Of the 42 oil medium studies, 3 were negative (1 disk L3 and L4; 1 disk L4 and L5; 1 negative exploration). Of the 9 air studies, 2 had both oil and air (1 negative on Roentgen ray study had a disk at L4 and L5).

It cannot be too strongly stressed that the radiologist who attempts these studies must be conversant with the various phases of the problem in order to attain a necessary technique and correct interpretations.

TABLE 2.—OPERATIVE FINDINGS AND RESULTS

Operative findings:
    Protruded disks only 40
    Hypertrophied ligamentum flavum 7
    Protruded disks and hypert. lig. flavum 6
    Herniation of annulus fibrosus 1
    Negative exploration 2
Location of protruded disks:
    L4–L5 23
    L5–S1 10
    L3–L4 8
    L2–L3 4
    D12–L1 1
    Multiple disks 5
Location of hypertrophied ligamentum flavum:
    L4–L5 7
    L5–S1 4
    L3–L4 1
    L1–L2 2
Results:
    Recovered 36
    Improved 6
    Unimproved (causes of failure in the 8 cases) 8
        Associated psychoneuroses 3
        Vascular disease of lower limbs 2
        Appearance of disk symptoms elsewhere . . . 1
        Associated degenerative disease of spinal cord . 1
        Cause unknown 1

Operative Findings and Results (Table 2). The location of the disks is quite in keeping with the larger statistics published by others. The negative explorations are not a source of great concern since these patients were operated on early in the experience of the surgeons and free manipulation was not used to extrude the injured disks.

Some of the cases of hypertrophied ligamentum flavum represented patients who were disabled for only a short time and who were operated against the choice of the senior author of this paper.

The results appeared gratifying in 36 of the 50 cases. Generally speaking, those who suffered longest and hardest gave the most gratifying results. But even among these 36, while the pain radiating down the leg was relieved, some backache remained, though not as a prominent symptom. Dr. Grant points out that prior to the operation the patient has so much suffering that he does not mind the slight backache due to the poorly functioning back which the operation did not correct.

One should not be overly optimistic about these results, however, as not enough time has elapsed to draw final conclusions.

Of the 8 failures, some of the patients had associated disease which may account for the continuation of the symptoms. These undoubtedly represent errors in diagnosis and judgment. In some cases, perhaps, adhesions were too extensive or formed again after operation.

Comment. *Problems in Diagnosis.* The analysis of the 50 cases operated upon indicates that the protruded disk and hypertrophied ligamentum flavum present fairly uniform historical data and objective abnormalities. It occurs most commonly in the fourth decade with a history of some form of trauma in more than 50% of cases. Low-back pain and pain in one or both extremities was recorded in most cases. This pain is mechanical in character with fairly constant aggravating factors. The average duration was over 4 years and intermissions were observed in more than half of the cases. The most constant objective abnormalities include the diminution of the lordotic curve, tilting of the pelvis, muscle spasm, positive Lasègue sign and alterations of the reflexes.

The above formulation is fairly uniform and suggestive but not pathognomonic of the protruded disk and hypertrophied ligament. Indeed, many other conditions have similar clinical history and objective abnormalities; in the final analysis, the diagnosis depends to a great extent, on the exclusion of other conditions. Therefore, before arriving at the diagnosis of a herniated disk, especially before advising operation, the clinician should be mindful of and rule out the following conditions, which can be conveniently divided into:

CONDITIONS TO BE CONSIDERED IN DIFFERENTIAL DIAGNOSIS. *Orthopedic Conditions.* Spinal anomalies, spondylolisthesis, sacro-iliac disease, lumbosacral disease, inflammations and neoplasms of the vertebral column, disorders of the articular facets, infections of the soft tissues (myositis, fibrositis, fasciitis), spasms of the fascia lata and pyriformis muscles.

Primary Neurologic Conditions. Neuritis, radiculitis, ganglionitis (including herpes zoster), lesions of the cauda equina and of the spinal cord, with special reference to specific infections and tumors.

Visceral Disease. Posterior peritoneal cavity and pelvis, especially lower genito-urinary tract, prostate and rectum.

Systemic Processes. Focal infections, deficiency states.

Psychalgias.

There are many pitfalls in diagnosis. The many and varied conditions which the protruded disk may simulate, requires the clinician to be conversant with the normal and abnormal structure and function of the various parts involved and a close familiarity with or at least consciousness of the many diagnostic problems. It is therefore surprising to learn that some clinicians regard the diagnosis of a protruded disk as a simple matter. To the authors it appears that the utter disregard of contrast medium studies prior to operation for the majority of cases is at present untenable.

Therapeutic Problems. It is evident that protruded disk has existed in most cases for a long time before the laminectomy and some patients must have got well without spectacular surgery. It is generally agreed by most neurosurgeons that the acute back condition, muscle spasm, tilting, and so on, is not a neurosurgical problem. Most of these cases recover with rest, traction, physical therapy, and so on. Most have no recurrences and some have mild recurrences which are a source of brief disability of varying degree.

Another consideration is the effectiveness of the laminectomy in relieving the disability produced by the protruded intervertebral disk. The analysis of the 50 cases indicates recovery in 36 cases, improvement in 6 cases and failure in 8 cases. These were operated on within the last $3\frac{1}{2}$ years and the end-result cannot yet be accurately estimated. It is possible that some cases, now apparently recovered, may have to be otherwise classified in the future. In this connection, the reports of other observers are of interest.

After considering these various factors, the authors feel that no case in which the diagnosis is reasonably certain, should be regarded as a desirable operative subject, unless (1) previous adequate orthopedic and other treatment was afforded for a reasonable time (3 to 6 months) without appreciable improvement in the disability; (2) the existence of moderate to major disability; (3) frequently recurrent brief major disability or recurrent moderate disability for considerable periods.

Summary. Fifty surgically treated cases of protruded intervertebral disk and hypertrophied ligamentum flavum were analyzed from the standpoint of history, objective abnormalities, special studies, operative findings and end-results. The problems of diagnosis, differential diagnosis and treatment were discussed.

Conclusion. Based on the experience with the 50 cases, the following criteria for diagnosis and indications for operations are suggested: (1) Exclusion of other definite causes; (2) suggestive history; (3) presence of at least some objective abnormalities; (4) previous adequate orthopedic and other treatment for a reasonable time (3 to 6 months) with no appreciable improvement in disability; (5) presence of a major disability; (6) lasting recurrent attacks of moderate disability or frequent attacks of major disability; (7) contrast medium studies prior to operation for the majority of cases.

REFERENCES

1. BRADFORD, F. K., and SPURLING, R. G.: The Intervertebral Disc, Springfield, Ill., Charles C Thomas, 1941.
2. CARNETT, J. B., and BATES, W.: Physiotherapy Rev., September and October, 1932.
3. DANDY, W. E.: J. Am. Med. Assn., 120, 605, 1942.
4. DEUCHER, W. G., and LOVE, J. G.: Proc. Staff Meet. Mayo Clin., 13, 697, 1938.
5. DOCKERTY, M. D., and LOVE, J. G.: Proc. Staff Meet. Mayo Clin., 15, 161, 1940.
6. FEILING, A.: Brit. Med. J., 1, 386, 1928.
7. KOCHER, T.: Mitt. a. d. Grenz. geb. d. Med. u. Chir., 1, 420, 1896.
8. LEWY, F. H., and GROFF, R. A.: Arch. Neurol. and Psychiat., 45, 373, 1941.
9. MIXTER, W. J., and BARR, J. S.: New England J. Med., 211, 210, 1934.
10. NAFFZIGER, H. C., INMAN, V., and SANDERS, G. B. DE C. H.: Surg., Gynec. and Obst., 66, 288, 1938.
11. VIETS, H. R.: New England J. Med., 189, 671, 1928.

THE EFFECT OF GLUCOSE ADMINISTRATION IN DIABETIC ACIDOSIS

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Introduction. The observations to be described were carried out to determine the effects of the administration of glucose to patients in diabetic coma. Even before the discovery of insulin, certain fundamental principles were successfully employed in the treatment of this complication of diabetes. The first was that the rapid metabolic rate in acidosis should be reduced by rest in bed and the use of a diet low in calories. Second, a decrease in the total amount of carbohydrate taken was used as a means of reducing the hyperglycemia and thus sparing pancreatic function. Third, treatment of the accompanying shock by the administration of adequate amounts of salt solution was considered essential. The object of treatment was primarily to improve carbohydrate metabolism, since it was recognized that ketosis, acidosis and finally clinical diabetic coma resulted from the primary disturbance in carbohydrate utilization. The introduction of insulin brought about immediate improvement in the results of management of diabetic coma and thus confirmed the tenet that control of carbohydrate metabolism is the essence of successful treatment. Yet fatalities still occur, usually in patients in whom outstanding features in the course of treatment have been the rise in blood sugar level in spite of insulin or the use of glucose solution intravenously or by mouth. That diabetic coma is a condition of acute insulin deficiency, the primary treatment of which is the provision of insulin in sufficient quantities, needs little demonstration. The administration of glucose by mouth and by vein therefore seems unreasonable unless it can be shown that glucose thus given is promptly oxidized, thereby reducing the rate of fat metabolism and ketogenesis, or else that the glucose thus given is stored as glycogen. If glucose thus administered merely accumulates in the intercellular body fluid, the question also arises whether this accumulation is harmless or whether under the conditions of diabetic acidosis the steady rise in the concentration of glucose in blood and intercellular fluid is actually harmful by bringing about a still greater degree of insulin deficiency. Our observations were carried out in the George F. Baker Clinic of the New England Deaconess Hospital primarily for the purpose of determining whether or not glucose given by vein or by mouth during diabetic acidosis is promptly oxidized.*

* The calculations of the carbohydrate burned were made in the usual empirical manner from the respiratory quotient and the total oxygen consumption. The value for total oxygen consumption was reduced by 15%, which was assumed to be the proportion of oxygen used in the combustion of protein, unless the urinary nitrogen was determined.

Case Studies. CASE 1 (19697) a laborer, developed diabetes in October 1940 at the age of 23 years and came for treatment in early acidosis December 2, 1940. No diabetic heredity known. Present weight 159 pounds dressed. His first urine specimen contained 6% sugar and 3+ diacetic acid. He immediately went to the metabolism room at 3:45 P.M. After he had rested 30 minutes, the respiratory helmet was put on. The results of determinations of oxygen consumption and respiratory quotient are shown in Table 1.

TABLE 1.—METABOLISM IN DIABETIC ACIDOSIS BEFORE AND AFTER INTAKE OF GLUCOSE

Case 1 (19697) Oxygen Consumption and Respiratory Quotient (R. Q.)

Period	Time, P.M.	R. Q.	O₂ per minute, cc.
1	4.30	0.632	370
2	4.40	.671	362
3	4.50	.700	349
	Average	.668	360 = 2429 cals. per 24 hrs. at R. Q. = 0.70

50 gm. glucose, 5.10—5.35 P.M., intravenously

4	5.55	.662	345
5	6.10	.680	330
6	6.25	.684	327
7	6.40	.666	333
8	6.55	.681	331

Predicted heat production (Harris-Benedict) was 1749 cals.
His actual heat production was thus 39.7% above prediction.

At the beginning of the test the blood sugar was 200 mg. and the CO₂ content of the venous blood was 25 volumes per cent. The value for total acetone bodies in the blood (including acetone, diacetic acid and beta oxybutyric acid) was 58 mg. per 100 cc.

It is obvious that in this case the respiratory quotient remained constantly at a level indicating little or no combustion of carbohydrate and that the administration of 50 gm. glucose intravenously did not raise the respiratory quotient during the hour and 45 minutes following the administration of glucose solution. No evidence of combustion of the glucose is present.

TABLE 2.—*Case 1 (19697)* METABOLISM FOLLOWING ADMINISTRATION OF INSULIN AND GLUCOSE

Period	Time, A.M.	R. Q.	O₂ per minute, cc.	CH combustion* per 15 min. gm.
	100 units crystalline insulin at 8:47 A.M.			
1	9.05	0.756	258	0.92 avg. for
2	9.15	.781	262	periods 1–3
3	9.25	.802	262	
	Average	.780	261 = 1795 cals. per 24 hrs. (R. Q. 0.78) = +2.6%	
	50 gm. glucose intravenously, 9.44–10.07 A.M.			
4	10.30	.871	266	2 36
5	10 45	.874	254	2.30
6	11.00	.895	266	2.77
7	11 15	.781	301	1.07
8	11.30	.694	320	0.00

* In calculation assumed 15% of O₂ consumption (avg. basal O₂) was due to protein combustion.

The contrast between the effect of glucose administration in acidosis and after recovery appears in the next observations. During the interval between his admission on December 2 in early acidosis and December 10 he received a diabetic diet containing carbohydrate 160 grams, protein 80 grams and fat 86

grams and an insulin dose that, during the days preceding the test on December 10, included 32 units of crystalline insulin and 36 units of protamine zinc insulin. On the morning of December 10 the metabolic observations in the subjoined table were made. One hundred units of crystalline insulin were given at 8:47 A.M. Then the respiratory quotient was determined during the fasting period. This was followed by the intravenous injection of 50 grams of glucose after which respiratory quotient measurements were continued for two hours.

It will be seen that the respiratory quotient promptly rose from 0.780 to a maximum of 0.895 at 11:00 A.M. Carbohydrate (CH) combustion per 15 minutes rose from a fasting level of 0.92 gm. to a maximum of 2.77 gm. It is evident then that this rather severe diabetic patient, when given an adequate supply of glucose and a large dose of insulin, rapidly increased carbohydrate combustion and at the maximum the rate per hour was approximately the same as in normal men subsequently cited.

The effect of hypoglycemia then appeared. In the period ending at 11:15 he began to sweat but did not seem uncomfortable. During the final 8th period he was sweating definitely, and the blood sugar, which had been 160 mg. fasting, was 50 mg. at 11:30 A.M. The striking feature is that with the onset of hypoglycemia the respiratory quotient rapidly fell to a level indicating cessation of carbohydrate combustion. He was then given orange juice and made a prompt recovery from the hypoglycemic reaction.

The important fact here is that with the onset of insulin hypoglycemia an extremely abrupt change in the type of metabolism may take place. One may conceive that with the fall in blood sugar further oxidation of carbohydrate is stopped by a reflex mechanism in order to conserve the glucose that is present and thus protect the highly sensitive tissues of the brain, which might otherwise suffer serious damage from prolonged hypoglycemia. Although the respiratory quotient of the brain of the depancreatized animal is 1.0,[3,6] indicating its ability to use carbohydrate without the presence of insulin, hypoglycemia caused by excessive insulin not only reduces the supply of glucose available in the blood but seems to affect the ability of the brain to utilize even that limited supply. In this case no acidosis was noted. The urine passed at the end of the experiment and during the rest of the day contained no diacetic acid, no doubt because the hypoglycemic reaction was terminated so quickly. It is generally agreed that long-continued or severe insulin hypoglycemia will result in loss of liver glycogen, although insulin administered to depancreatized animals characteristically increases glycogen deposition in the liver from a low to a normal amount. In brief periods of insulin hypoglycemia the liver glycogen may be high, as in Case 6884, age 25 years, with diabetes of 11.7 years' duration. A biopsy of the liver revealed a fat content of 10.5% and a glycogen content of 12.1%. The respiratory quotient determined 1 hour before the biopsy was 0.82, and the blood sugar was 33 mg. No symptoms of hypoglycemia had occurred, indicating that the reflex mechanism associated with typical symptoms of hypoglycemia had not been aroused. In summary, we may say that in Patient 19697 during acidosis, glucose administered was not oxidized. After recovery from coma and after treatment with diet and insulin had been carried out for some days, when an excess of insulin was given such that an insulin reaction resulted in spite of the provision of an excessive amount of glucose, the amount of carbohydrate combustion at its peak did not exceed the rate of 11 gm. per hour.

CASE 2 (20239) developed diabetes in May 1941 at the age of 14 years. He came for treatment on June 16, 1941, in early diabetic coma. His urine contained 3.4% sugar and 3+ diacetic acid. Early Kussmaul respiration was present. He entered the metabolism laboratory at 4:55 P.M. and the respiration helmet was put in place at 5:25 P.M. for the first 3 periods. The blood sugar at 6:18 P.M. was 230 mg., the CO_2 content of the venous blood was 18 volumes per cent, and the acetone bodies were 70 mg. per 100 cc. Intravenous administration of 50 gm. of glucose was begun at 6:25 P.M. At 8:00 P.M. the blood sugar had risen to 370 mg., and the CO_2 content of the blood was 21 volumes per cent,

Following the administration of 30 units of crystalline insulin at 8:05 P.M., the blood sugar fell at 9:00 P.M. to 180 mg. and the CO_2 value of the blood rose to 23 volumes per cent. He then received an additional 8 units of insulin at 10:00 P.M., and the next morning his fasting blood sugar was 60 mg., the CO_2 content of the blood was 38 volumes per cent, and the respiratory quotient was 0.72. In Table 3 are shown the individual values for the respiratory quotient and oxygen consumption in the preliminary periods before the administration of glucose, then those in a series of three periods following the intravenous injection of glucose, and finally those in 3 periods following the injection of insulin. In these last 3 periods there was a gradual, slight rise in the respiratory quotient.

TABLE 3.—*Case 2 (20239)* OXYGEN CONSUMPTION AND RESPIRATORY QUOTIENT IN COMA BEFORE AND AFTER ADMINISTRATION OF GLUCOSE AND INSULIN

Period	Time, P.M.	R. Q.	O_2 per minute, cc.	CH Combustion per 15 min. (gm.)
1	5.40	0.678	216	
2	5.50	.673	215	
3	6.00	.672	222	
	Average	.674	218 = 1471 cals.	0.0

Intravenous dextrose (50 gms.), 6:25–6:52 P.M.

Period	Time, P.M.	R. Q.	O_2 per minute, cc.	CH Combustion per 15 min. (gm.)
4	7.05	.661	208	0.0
5	7.20	.679	206	0.0
6	7.35	.688	207	0.0
	Average	.676	207	

30 units crystalline insulin intravenously, 8:05 P.M.

Period	Time, P.M.	R. Q.	O_2 per minute, cc.	CH Combustion per 15 min. (gm.)
7	8.15	.672	222	0.0
8	8.30	.687	219	0.0
9	8.45	.712	220	0.0
	Average	.690	220	

His heat production, predicted from the Harris-Benedict formula for men, is 1240 cals., and predicted from Table 20 in Pub. 303A, Carnegie Institution of Washington, it is 1236 cals.; thus his heat production was 18.6% above prediction.

Intravenous administration of glucose in this boy was not followed by any significant change in respiratory quotient or any evidence that the glucose was utilized. A decline in blood acetone occurred without a rise in respiratory quotient. The total blood acetone values fell from 70 mg. at 6:00 P.M. to 58 mg. at 8:00 P.M., 44 mg. at 9:00 P.M. and 28 mg. when he was fasting the next morning. The administration of insulin, however, brought about a slight rise in respiratory quotient, which was immediate and was still evident 12 hours later. At 9:15 P.M., 1066 cc. of urine were voided, the first urine voided after the urine that was voided at the beginning of the observation at 4:00 P.M. This urine contained 3.3% sugar, a total excretion of 35.2 gm. The nitrogen present was 4.4 gm. The next specimen, voided at 10:15 P.M., showed only a trace of sugar. We may then assume that the 35 gm. of glucose represented the total loss of glucose following the injection of 50 gm. of glucose in the metabolism test. In such a case, with early diabetic coma, recovery would probably have occurred without the use of insulin, as was occasionally true in the years prior to the discovery of insulin. The first factor that was effective was rest in bed and a restriction of diet in total calories so that the high metabolic rate was steadily reduced. This one factor alone in the early stage of acidosis will reduce the amount of fat catabolism and so reduce the amount of ketone body formation. In this case, the oxygen consumption fell during the periods from 7:05 to 7:35 P.M. as compared with the first 3 periods. A simultaneous fall in blood acetone values occurred. With the use of insulin the usual rise in oxygen consumption after glucose was observed. In this case there is no evidence for believing that any of the glucose injected was oxidized.

During acidosis the energy requirements are greatly in excess of the normal rate, as shown by our observations on patients in diabetic coma whose metabolic rates have varied between 20% and 48% above normal. To meet this high caloric need, some fat oxidation undoubtedly occurs in the muscles themselves. However, a considerable fraction, probably from one-third to one-half, of the total needs from fat is obtained by a preliminary oxidation of fat in the liver to ketone bodies only. Neither acetic acid nor glucose is formed by this oxidation. These ketone bodies are, under ordinary circumstances, freely utilized for energy by the peripheral tissues without insulin. When the demand for calories from fat exceeds a level of approximately 2.5 gm. of fat per kg. body weight per day in a resting state, ketone bodies in excess of needs are formed by the liver.[13] If this excessive fat catabolism continues unchecked, ketosis and coma follow. That a fairly close parallel exists between the degree of acidosis and the degree of elevation of the metabolic rate was shown by Joslin.[7] In our patients, then, with acidosis we find an excessively high metabolic rate, the caloric needs for which are met almost entirely from fat and in these patients no improvement in the type of metabolism will occur until a sufficient quantity of insulin, endogenous or exogenous, is available to make carbohydrate combustion take its normal place. The metabolic rate of Case 20239 was 61 calories per hour. The nitrogen excretion, a total of 4.4 gm. in 9 hours, equalled 0.5 gm. per hour, which is equivalent to a protein metabolism of 3.1 gm. per hour. We assume 12 calories from protein and subtract this from 61 calories per hour, which leaves 49 calories to be derived from fat, which would mean a rate of 131 gm. per day. His weight was 35 kg., so that this would greatly exceed the rate of 2.5 gm. of fat per kg. body weight postulated by Stadie.[13] Effective insulin action in acidosis results in a reduction of the metabolic rate and in his case the fall in oxygen consumption was from +18.6% (June 16, 5:40 p.m.) to 3.2% above the standard as measured the following morning.

TABLE 4.—EFFECT OF INSULIN UPON CARBOHYDRATE COMBUSTION

Period	Time, P.M.	R. Q.	O_2 per minute, cc.	CH combustion per 15 min., gm.
1	1 10	0 709	299	
2	1 20	701	309	
	Average	705	304	0 00
	10 units crystalline insulin at 2 20 p.m.			
3	2 40	713	296	0 00
4	2 55	731	296	0 29
5	3 10	717	305	0 62
	Rest period			
6	4 05	731	287	0 17
7	4 20	733	296	0 29
8	4 35	727	296	0 67
	Rest period			
9	5 45	723	292	0 64
10	6 00	735	297	0 23
11	6 15	727	294	0 19

CASE 3 (20945), school boy, age 15 years, demonstrates the effect of insulin alone upon the respiratory quotient during acidosis. He came for treatment on January 21, 1942, with diabetes which had just been discovered. Upon arrival the urine contained 8.7% sugar, 4+ diacetic acid and the CO_2 of the blood was 31 volumes per cent. He was sent to the hospital at noon. The respiration helmet was placed at 1:10 P.M. Forty units of crystalline insulin were given at 2:20 P.M. and a series of observations was carried on ending at 6:30 P.M. The blood sugar was 360 mg. on admission and 101 mg. at the end of the observation. The data are summarized in Table 4.

During the period of study a marked change in nitrogen excretion in the urine occurred as shown in Table 5:

TABLE 5.—*Case 3*. NITROGEN AND CREATININE ELIMINATION IN DIABETIC ACIDOSIS

				Nitrogen eliminated			Creatinine eliminated		
	Collection Period			Per		Per	Per		Creat.
			Vol.,	cc.,	Total,	hour,	cc.,	Total,	coeffi.,
Date 1942	Start	End	cc.	mg.	gm.	mg.	mg.	mg.	mg./kg./24°
Jan. 21	11.00 A.M.	1.45 P.M.	780	3.91	3.05	1109	0.46	361	67.4
" "	1.45 P.M.	3.45 P.M.	258	5.50	1.42	710	0.52	134	34.5
" "	3.45 P.M.	6.30 P.M.	100	10.63	1.06	387	1.58	158	29.4
Jan. 21, 6.30 P.M., to Jan. 22, 7.00 A.M.			520	8.14	4.23	339	0.90	470	19.3
Total for 24 hours			1990	5.88	11.71	488	0.68	1348	28.8

It is evident that during the period from 11:00 A.M. to 1:45 P.M. the nitrogen elimination per hour was at the rate of 1109.1 mg. During the next 2 hours the rate fell to 710 mg. and during the period from 3:45 P.M. to 6:30 P.M. the elimination fell to 387 mg. per hour. During the next 12 hours this rate fell to 339 mg. During these same periods a comparable change in creatinine elimination was observed with the result that the creatinine coefficient fell from 67.4 to 19.3 mg.

This case indicates that the use of insulin alone in a patient with early diabetic acidosis will increase carbohydrate consumption even when only a small dose, such as 40 units, is given. The fact is that only a small amount of increase in glucose oxidation is necessary. Heat production in this patient was at the rate of 85.5 calories per hour. Carbohydrate oxidation amounted to 0.47 gm. in 45 minutes of the last 3 periods. Thus approximately 2.5 calories per hour were obtained in the oxidation of glucose.

Rate of Oxidation of Glucose in Normal Subjects. The rate of the utilization of injected or ingested glucose in the normal individual is low; in the resting state only between 6 and 12 gm. per hour are oxidized. Therefore, in any consideration of the part played by the oxidation of glucose in diabetic patients normal standards must be considered. A normal male, 43 years of age, weight 66.8 kg., who ingested amounts of glucose varying from 5 to 104 gm. was studied by Carpenter and Fox.[4] Their results clearly show that in the majority of the observations the greatest rise in respiratory quotient indicating the greatest increase in carbohydrate combustion was observed during the third half hour following the ingestion of the glucose. All amounts of 10 gm. or more were followed by significant changes in the respiratory quotient. The striking fact, however, was that no close relationship was found between the amount of glucose ingested and the increase in grams of carbohydrate oxidized per hour. Thus, after the subject received 15 gm. of glucose, the carbohydrate metabolized during the first 2 hours was 14.25 gm. which represents an increase over the fasting rate of 3.17 gm. When he received 25 gm. of glucose, the amount of carbohydrate metabolized in the same first 2 hours was 16.2 gm., an increase of 4 gm. When he received 104 gm. of glucose, the carbohy-

drate metabolized during the same 2 hours totaled 18.8 gm., an increase of 10.3 gm. The facts regarding this normal man are so important that they are summarized in Table 6. It is evident that in the first 3½ hours following the ingestion of 104 gm. of glucose, when his fasting or basal respiratory quotient was 0.81, the total carbohydrate metabolized was 35.4 gm. The same point appears in the studies of normal young men receiving 50 gm. of glucose by mouth and by vein, reported by Root and Carpenter.[11] The *increases* in carbohydrate combustion during 2¼ hours after the administration of 50 gm. of glucose averaged in 4 subjects 10.6 gm. by the oral route and 9 gm. when the glucose was given intravenously. Therefore, in our observations of diabetics, it is important to remember that even in normal individuals, no matter how much glucose is given by vein or by mouth, in a resting state only between 6 and 12 gm. per hour are oxidized. Obviously if extreme muscular exertion is being carried out, glucose oxidation will be increased.

TABLE 6.—OXIDATION OF GLUCOSE BY A NORMAL MAN[4]

	Carbohydrate Combustion (gm. per half hour)
Basal	2.13
Half hours after 104 gms. glucose	
1	3.33
2	5.31
3	5.20
4	5.01
5	4.85
6	6.16
7	5.58
Total	35.44

Total increase over basal 20.2 gm.

Harmfulness of Excessive Glucose During Diabetic Coma. Not only is the administration of large amounts of glucose useless and ineffective in diabetic acidosis, but such a procedure may be positively harmful in that (1) a rise in blood sugar produced by glucose will make it difficult to determine the required insulin dosages by changes in the blood sugar; (2) such excessive hyperglycemia is always harmful to the pancreas; (3) excessive glucose concentration in the blood and tissues under the conditions of acidosis has been known to result in anuria;[5] (4) the experiments of Astwood, Flynn and Krayer[1] indicate that excessive glucose may lead to damage in the liver. Recently a most valuable contribution to the study of this problem appeared in a case reported by Grunberg and Rhodes.[3] Their patient, a boy, age 15 years, had been under observation as an out-patient for 6 months with a blood sugar content varying from 120 to 240 mg. per 100 cc. He was admitted in diabetic coma at 12:30 P.M. with semi-consciousness, dry skin, soft eyeballs, blood pressure systolic 70, diastolic 50, blood sugar 425 mg., urine sugar 3%, and gross ketonuria. Table 7 summarizes the insulin dosage, blood sugar values, and glucose administration. The boy did not seem in far-advanced coma, as he was not entirely unconscious and was not pulseless. Furthermore, anuria was not present. The

extraordinary feature was that this case of coma should have advanced to such a condition at 1 A.M. the following morning that the authors felt that he was moribund. At 3 A.M. it was believed "that he would be dead in an hour or two." As we analyze the table, it is evident that he received 175 gm. glucose at the outset of his treatment when only semi-conscious and in spite of a dose of 215 units of insulin during that same period the blood sugar had risen to 600 mg. by 5 P.M. Thereafter the blood sugar continued to rise in spite of generous insulin dosage, until finally a sufficient insulin dose brought about recovery. It is instructive to make a calculation of the relation between the glucose administered by mouth and by vein and the grams of glucose present in the intercellular fluid,* as represented by the increase in blood sugar concentration from 425 to 1600 mg. The boy's weight was 36 kg. We may assume that the intercellular fluid was roughly 25% of his weight or about 9 liters. An increase in blood sugar of 1175 mg. per 100 cc., when applied to this volume of intercellular fluid, would indicate that there had been a total increase in glucose in this fluid of 105 gm. This increase in glucose alone would greatly increase the requirement of insulin. If we return to the figures for diabetic patients and for normals, we find that the most one can hope for is combustion of from 5 to 10 gm. of glucose in the first 2 hours of the emergency in diabetic coma. The administration of more glucose when the blood and intercellular fluid already contain glucose in excessive amounts can have no possible benefit, unless there is a previous administration of insulin in such amounts as will surely compel glucose utilization. This boy strikingly illustrates the fact that recovery in diabetic coma occurs when carbohydrate utilization takes place at such a rate that the concentration of glucose in the blood and intercellular fluid falls rather than rises. The administration of excessive amounts of glucose imposes such a burden on the insulin injected as to retard and impede its action. In the last series† of 73 successive coma cases with blood CO_2 of 20 volumes per cent or less, at the New England Deaconess Hospital reported by Joslin, Root, White and Marble,[8] no fatalities have resulted, and we still feel that although the absence of complications fatal in themselves in this group of cases cannot be ignored, emphasis upon the rapid administration of insulin in doses sufficient to bring about utilization of the excessive glucose already present in the blood as indicated by a fall in the blood sugar within the first 5 or 6 hours, the administration of sufficient fluid in

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* An increase of blood sugar from 425 to 1600 mg/100 cc., means an increase of 65 millimols per liter of fluid. If this is superimposed upon the usual osmolar concentration of body fluids of 320 mM/L, that would mean an osmolar concentration of 385 mM/L, or a markedly hypertonic solution, and a consequent shrinking of cells generally, unless the intracellular fluids of the tissues become hypertonic at the same time to the same degree. If one were to assume that the glucose was uniformly distributed through the water of the tissue, both intracellular and extracellular, one might figure that he had 293 gm. more sugar in his body fluids at 1:10 A.M. than at 12:30 P.M. This is assuming that there was 25 kg. of H_2O in a 36 kg. boy, and all the water had increased its sugar content 11.75 gm. per kg. Whether glucose is distributed thus uniformly through the tissues of the body is not yet known.

† In the original report the number of successive cases of diabetic coma without fatality was 62, but has since risen to 73.

the form of physiologic salt solution and the inauguration of hourly feeding from the 6th hour onward were the essential factors in the treatment.

TABLE 7.—EXTREME HYPERGLYCEMIA FOLLOWING ADMINISTRATION OF GLUCOSE IN DIABETIC COMA, BOY, 15 YRS.[5]

| Time | Blood sugar, mg. | Glucose (grams) | | Insulin (units) | | Clinical condition |
		By mouth	Intra-venously	Subcu-taneous	Intra-venously	
12 30 P.M.	425	..	..	...	..	Semi-conscious
1–5 P.M.	600	150	25	140	75	
5–8.40 P.M.	1040	20	..	100	300	Unconscious
9–11 30 P.M.	920	..	..	..	800	
1 10 A.M.	1600	..	..	.	...	Moribund
1 30–3 A.M.	...	..	..	..	800	
9 00 A.M.	160	...	..	..	..	Better
11 00 A.M.	65	40				
12 30 P.M.	112					
1 30 P.M.	...	...	..	...	..	Almost conscious
2 10 P.M.	180	160				

Causes of Diabetic Acidosis. Undoubtedly deprivation of insulin is the most frequent factor precipitating diabetic coma, but also it must not be forgotten that deprivation of insulin may mean not the omission of a dose of insulin but merely that the patient's own supply of endogenous insulin has become inadequate for increased metabolic needs, as in cases of diabetic coma developing before the diagnosis of diabetes has been made. Or a constant supply of insulin may become inadequate by virtue of a great increase in the total metabolism or by influences such as infection or exhaustion or hyperglycemia with the associated changes in the tissues that impair glycogen storage. There can be no doubt that in some mild diabetic patients the addition of carbohydrate may stimulate insulin production and increase in a limited way the amount of carbohydrate retained. There is no evidence that this is the case in serious cases of diabetic acidosis. Any complication that accelerates the loss of glycogen in the liver, such as hyperthyroidism, endocrine disturbances, infection, anesthesia, nausea, vomiting, will contribute to severity and rapid development of diabetic coma. However, glycogen starvation of the liver without diabetes, as it is observed in fasting or intense hyperthyroidism, never produces a condition resembling diabetic coma. It is only when insulin deficiency is present that glycogen impoverishment in the liver becomes an important element in the clinical state. It is too commonly forgotten that the administration of glucose in large amounts producing hyperglycemia has an exhausting effect upon the islands of Langerhans,[2] still further diminishing their insulin-producing function, and, furthermore, that it is possible with excessive administration of glucose in animals, as shown by Astwood, Flynn and Krayer[ ] at the Peter Bent Brigham Hospital, to produce actual destruction of liver tissue.

Summary. 1. In diabetic coma the administration of glucose solution either intravenously or by mouth does not result in an increase in respiratory quotient indicating any increase in carbohydrate combustion.

2. Insulin produces an increase in carbohydrate combustion, indicated by a rise in respiratory quotient.

3. Even with insulin administration there is no evidence that more than 10 gm. of carbohydrate can be or need be oxidized per hour, in order to reduce the rate of fat metabolism and so to check the process of ketone body formation.

4. The harmful effect of glucose may be concealed in early diabetic coma by the favorable effects of insulin simultaneously administered; the moderate case of coma may be converted into a severe one requiring excessive insulin dosage. In advanced coma, glucose administration may precipitate the final stage of anuria.

5. The object of treatment in diabetic coma is to restore normal utilization of carbohydrate by the administration of the requisite amount of insulin. By this means, the excessive glucose in blood and tissue fluids is oxidized or stored, liver glycogen is replenished and excessive ketosis is reduced by a reduction in the rate both of total metabolism and of fat oxidation.

REFERENCES

1. Astwood, E. B., Flynn, J. M., and Krayer, O.: J. Clin. Invest 21, 621, 1942.
2. Baker, Z., Fazekas, J. F., and Himwich, H. E.: J. Biol. Chem., 125, 545, 1938.
3. Best and Taylor: Physiological Basis of Medical Practice, 3d ed., Williams & Wilkins Co., Baltimore, p. 894, 1943.
4. Carpenter, T. M., and Fox, E. L.: J. Nutr., 2, 375, 1930.
5. Grunberg, A., and Rhodes, A. J.: Edinburgh Med. J., 49, 394, 1942.
6. Himwich, H. E., and Nahum, L. H.: Am. J. Physiol., 101, 452, 1932.
7. Joslin, E. P.: Diabetic Metabolism with High and Low Diets, Washington, Carnegie Institution of Washington, Pub. 323, pp. 77, 78, 80–82, 84, 1923.
8. Joslin, E. P., Root, H. F., White, P., and Marble, A.: J. Am. Med. Assn., 119, 1160, 1942.
9. Lukens, F. D. W., and Dohan, F. C.: Endocrin., 30, 200, 1942.
10. Richardson, H. B.: Physiol. Rev., 9, 61, 1929.
11. Root, H. F., and Carpenter, T. M.: Arch. Int. Med., 69, 997, 1942.
12. Root, H. F., and Riseman, J. E. F.: J. Am. Med. Assn., 110, 1730, 1938.
13. Stadie, W. C.: Ann. Int. Med., 15, 783, 1941.

CORRELATION OF THE INTRAVENOUS HIPPURIC ACID TEST OF LIVER FUNCTION WITH BODY SIZE

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The excretion of hippuric acid after the administration of sodium benzoate, formerly intended as a measure of renal function,[3,6] has been studied extensively by Quick.[8,9] In 1933 he proposed it as a test of liver function.[10] After some delay this test has received increasing attention.

Quick showed[8] that, regardless of the amount of sodium benzoate given, beyond a certain minimal quantity, and in the absence of exogenous glycine, a relatively constant amount of hippuric acid will be excreted in the urine. With an adequate dose of sodium benzoate, the amount of hippuric acid formed depends primarily upon the capacity for synthesis of glycine, presumably in the liver, and also upon the capacity to conjugate it with benzoic acid.

Quick[8] stated that the rate of synthesis of glycine appeared to be a constant, depending on the size of the individual. He later[11] stated that the rate of excretion of hippuric acid is influenced only somewhat by the size of the subject. As it was planned,[10] a maximal load was supposed to be placed on the liver by the hippuric acid test. Presumably every cell is forced to its greatest capacity in the synthesis of glycine for conjugation. It seemed, therefore, that the rate of formation of hippuric acid should vary normally with the size of the liver. If this is so, it seemed that a variable standard of normal hippuric acid excretion, based upon the size of the subject, would be more accurate than a single constant standard.

There are no adequate data available to indicate which body measurement—weight, height ("normal" weight), or surface area—would be the most accurate basis for prediction of normal liver size and consequently the expected excretion of hippuric acid. We have calculated from the data of Greenwood and Brown[5] of 78 cases with "normal organs" that those having body weights within 25 pounds of the predicted normal (most subjects were below normal weight) had livers averaging 35.6 ounces per square meter of surface area or 0.433 ounce per pound. Those who were more than 25 pounds underweight had livers averaging 32.7 ounces per square meter or 0.455 ounce per pound. There was, however, such a very wide range in the ratios of liver weight to body size that these figures are not significant.

Boyd,[2] in a statistical study of 312 cases dying within 24 hours of accident or similar causes without gross hemorrhage and without other significant disease, reported that the liver is essentially stationary in weight from 20 to 55 years and then decreases in weight. The possible significance of this will be referred to later although correlation with body size was not made. Bean and Baker[1] reported that the liver of the negro is smaller than that of the white man.

Because of a frequency of nausea (and sometimes vomiting), greater than has commonly been reported, among our first series of normals to whom sodium benzoate was given orally, the intravenous route more recently proposed by Quick, Ottenstein and Weltchek[11] was used for subsequent tests. The results obtained with this type of test dose are the basis of this report.
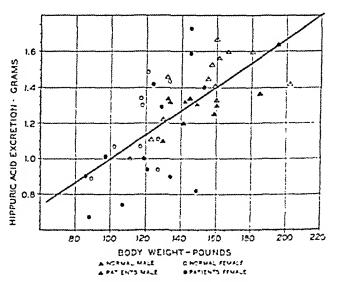
Method. The tests were done in the morning after a breakfast of tea or coffee, as advised by Quick.[11] Sodium benzoate (1.77 gm. in 20 ml. of water) was injected intravenously over a period of 5 minutes (and urine specimens collected 1 hour after the completion of the injection as recommended by Quick, Ottenstein and Weltchek.[11] Hippuric acid was determined by the simpler clinical method of Quick,[9] except that ammonium sulfate was added before precipitating the acid so that separately a freed [?]

TABLE 1.—DATA ON THE INTRAVENOUS HIPPURIC ACID TEST ON SUBJECTS
UNDER 55 YEARS OF AGE

Case	Diagnosis	Sex	Age (yrs.)	Ht. (in.)	Wt. (lbs.)	Surface area (sq. m.)	Hippuric acid excreted (gm.)	Predicted excretion (surface area)	% of predicted excretion (surface area)	Predicted excretion (lbs.)	% of predicted excretion (lbs.)
1	Student	M	24	76¾	202.0	2.21	1.36	1.69	84.1	1.69	84.1
							1.48				
							1.42 Av.				
2	Student	M	21	73.0	195.5	2.11	1.64	1.60	102.4	1.64	100.0
3	Instructor	M	31	74.5	180.0	2.08	1.73				
							1.48				
							1.60 Av.	1.585	100.9	1.54	104 0
4	Student	M	24	76.5	166.0	2.02	1.66				
							1.53				
							1.60 Av.	1.523	105.0	1.45	110.3
5	Duodenal ulcer	M	46	71.0	185.0	2.02	1.37	1.523	90.0	1.58	86.7
6	Instructor	M	27	73.5	160.0	1.95	1.33	1.47	90.5	1.41	94.3
7	Student	M	24	72.0	160.0	1.92	1.31				
							1.28				
							1.30 Av.	1.445	89.9	1.41	92.2
8	Student	M	24	70.5	161.0	1.88	1.57	1.41	111.3	1.415	111.0
9	None	M	34	70.0	159.0	1.88	1.25	1.41	88.6	1 40	89.3
10	Student	M	22	72.0	155.0	1.90	1.45	1.43	101.3	1.375	105.5
11	Student	M	23	70.5	160.0	1.89	1.67	1.42	117 7	1.41	118.4
12	Student	M	25	70.5	159.0	1.87	1.41	1.40	99.2	1.40	100.7
13	Student	M	23	68.5	157.0	1 84	1.53	1.38	110.8	1.39	110.0
14	Duodenal ulcer	M	30	70.0	148.5	1.82	1.31	1.36	96.4	1.33	98 5
15	None	M	42	69.0	145.0	1.78	1.34	1.33	100.7	1.31	102 2
16	Psychoneurosis	F	32	66.0	153.0	1.76	1.40	1.31	106.9	1.36	102.9
17	C.N.S. disease	M	22	68.0	142.0	1.75	1.32	1 31	100.6	1.29	102.3
18	Uterine fibroid	F	35	65.0	145.0	1.71	1.59	1.27	125.3	1.31	121.3
19	Compound fracture	M	16	66.0	141.0	1.71	1.20	1.27	94.5	1.28	93 7
20	Asthma	M	16	67.0	134.0	1.69	1 33	1.252	106.2	1.236	107.6
21	Student	M	23	66.5	132 0	1.67	1.59				
							1.33				
							1.46 Av.	1 235	118 2	1.22	119.7
22	None	F	29	62.0	149.0	1.67	0.82	1.235	64.4	1.335	61.4
23	Chronic pelvic disease	F	29	63.0	134.0	1.67	0.90	1.235	72.8	1.236	72.8
24	Lues—liver neg. at postmortem	M	53	66.5	130.0	1.66	1.22	1.223	99.7	1.21	100.8
25	Allergic bronchitis	F	30	64.0	124.0	1.66	1.42	1.225	115.8	1.17	121.3
26	Mild obesity	F	40	62.0	145.0	1.65	1.73	1.22	141.7	1.31	132.0
27	Duodenal ulcer	M	38	64.5	134.0	1.64	1.32	1 21	109.0	1.236	106.8
28	Duodenal ulcer	M	40	66 0	130.0	1.64	1.10	1.21	90 0	1.21	90.9
29	Dietitian	F	25	66 5	127.0	1.64	0.94	1 21	78.0	1 19	79.0
30	Nurse	F	20	63.5	133.0	1.62	1 44	1.195	120.0	1.23	117.0
31	Dietitian	F	25	65.0	127.0	1.62	1.11	1.195	93.0	1 19	93.3
32	Mild pelvic inflam. dis.	F	21	67.0	119 0	1.60	1.00	1.177	84.9	1.135	88.1
33	Student	M	26	64.0	123.0	1.57	1.11	1.15	96.5	1 16	95.7
34	Technician	F	28	65.0	118.0	1.57	1.30	1.15	112.7	1.13	115 0
35	Arthritis	F	39	64.0	121.0	1.57	0.94	1.15	81 7	1.15	81.7
36	Subarachnoid hemorr.	F	22	61.0	129.0	1.55	1.29	1.135	113.7	1.20	107 5
37	Technician	F	23	63.5	121.0	1.55	1.49	1.135	131 0	1.15	132 3
38	Clinic clerk	F	30	64.0	117.5	1.54	1.34	1.123	119.3	1.125	119.2
39	Bronchiectasis	F	18	65.0	106.5	1.50	0.74				
							0.74				
							0.74 Av.	1.090	67.9	1.05	70 5
40	Clinic clerk	F	27	60.0	117.0	1.47	1.07	1.065	100.5	1.12	95.5
41	Nurse	F	22	61.0	111.0	1.46	1.00	1 06	94.4	1 08	92 6
42	Anxiety	F	15	62.0	102.0	1.43	1.07	1.033	103 6	1.025	104.3
43	Pneumonitis	F	18	62.0	97.0	1.38	1.01	0.99	101 9	0 99	102 0
44	Subacute rheum. fever	F	23	63.0	87.0	1.34	0.65	0.96	67.7	0.92	70.7
45	Clinic clerk	F	27	62.0	89.0	1.34	0.89	0.96	93.1	0.93	95.8
46	Anxiety	F	28	63.0	86.0	1.33	0.90	0.95	94 7	0.91	99.0

Results. The intravenous hippuric acid test was performed upon 46 subjects, mostly young adults; 23 were males and 23 females. Twenty-two subjects were students or staff members in presumably good health and 24 were patients without apparent liver disease. The excretion in these subjects varied from 0.65 to 1.75 gm. of hippuric acid in 1 hour (Table 1). We have preferred to dispense with the conversion of these figures into their equivalents of benzoic acid.

The results of these tests have been studied statistically. No difference in the excretion for the sexes was found. The amount of hippuric acid excreted was compared with the body weight, height, ideal weight as obtained from insurance tables, and surface area. A definitely significant correlation between the hippuric acid excretion and both body weight and surface area was found, the correlation being almost identical for the two factors.

CHART 1. — The excretion of hippuric acid in 1 hour after the intravenous injection of 1.77 gm. of sodium benzoate by 46 normal subjects and patients without liver disease under 55 years of age.

all of the subjects used were of about normal weight. It is possible that with a sufficient number of tests upon subjects with a wider range of body build, a preference would be established for the use of body weight or surface area as a basis for normal standards.

Of the normal subjects, 90% excreted between 72.8% and 125% of the predicted normal amounts of hippuric acid. This is a rather wide range of apparent hepatic function. The range of normal values based upon these determinations would, however, need to be much larger if the normal standard were not based upon body size. The 5 largest subjects excreted an average of 1.53 gm. of hippuric acid while the 5 smallest subjects excreted an average of only 0.9 gm. Although 3 subjects excreted somewhat less than 70% of the normal amount of hippuric acid predicted on the basis of surface area and 1 subject, less than 70% of that predicted on the basis of body weight, we would consider that figure (70%) the borderline of normal excretion with this test in subjects between the ages of 20 and 55 years.

TABLE 2.—HIPPURIC ACID EXCRETION IN PATIENTS OVER 55 YEARS WITHOUT KNOWN LIVER DISEASE

Diagnosis	Age	Sex	Height (in.)	Weight (lbs.)	Ideal weight (lbs.)	Hippuric acid	
						Excreted	% of predicted excretion
Hypertension	58	M	68	142	154	0.95	74
Cancer of larynx	70	M	69	139	158	0.92	73
Nucleus pulposus	56	M	71	159	168	1.13	80
Cancer of lip	64	M	71	184	168	1.04	64
Cord tumor	60	F	63	186	128	0.67	41
Peptic ulcer	64	M	..	120	..	1.01	90

Tests were done on 6 additional patients of 56 years or over who had no apparent evidence of liver or kidney disease. They excreted an average of 70.3% of the amount of hippuric acid predicted from their surface area (Table 2). This suggests that in older age groups there is physiologically some atrophy of the liver which causes some impairment in the response to the hippuric acid test of liver function. This is in accord with the findings of Boyd[2] although, as was noted, the liver weights in her series were not correlated with body size. The effect on her figures of the influence of relative weight on longevity is consequently not known.

No serious complications resulted from the slow intravenous injection of sodium benzoate. Many patients have noted an aching sensation along the course of the vein, particularly when the injection was given more rapidly. Two subjects, among this group and other patients on whom the test was done, have had sudden severe abdominal cramps sufficient to cause interruption of the test. In one allergic individual, a moderately severe urticaria developed immediately after the injection and lasted about 1 hour. We have also seen urticaria appear after the oral administration of sodium benzoate and have noted the occurrence of allergic types of reactions following the intravenous injection of bromsulphthalein.

The chief advantage of the intravenous hippuric acid test is that it avoids the nausea and vomiting which occurred frequently in our normal subjects. This has been particularly helpful in performing the

tests on patients who already have abdominal symptoms. The intravenous administration also eliminates the factor of absorption from the gastro-intestinal tract and shortens the test.

The possible disadvantage of the intravenous method is the greater effect on the result of inaccuracy in collecting completely a 1 hour specimen rather than a 4 hour specimen of urine. It is probable that some of the variability of results in this series was due to incomplete emptying of the bladder. This source of error may be minimized by provision for an adequate urine volume. Several of our patients, not in this series, with 1 hour urine volumes of 10 to 15 cc. had small excretions of hippuric acid which subsequently were normal when the preliminary fluid intake was increased. The test is, of course, of no value when there is significant urinary bladder retention unless the bladder is catheterized.

The value of the hippuric acid test of liver function presupposes an adequate renal function. Snapper and Grünbaum[14] have been quoted that the excretion of hippuric acid was normal in cases without retention of urea. Their series was small and, with 12 hour urine specimens, delays in excretion could have been overlooked. Kohlstaedt and Helmer[7] found a subnormal excretion of hippuric acid in 9 subjects with urea clearances of 50% or less, 4 of whom had no evidence of liver disease. Quick[8] has shown that there was more than a 50% increase in hippuric acid excretion when glycine was taken with the sodium benzoate, indicating at least that much greater normal capacity for renal excretion over the synthesis of hippuric acid.

Campbell[1] has shown that patients who have been depleted of glycogen postoperatively have decreased excretions of hippuric acid which quickly return to normal following restoration of carbohydrate.

Summary. The excretion of hippuric acid following the intravenous injection of sodium benzoate as a test of liver function in 46 subjects without apparent liver disease has been found to be influenced decidedly by the size of the subjects.

Formulæ for the predicted normal excretion of hippuric acid, based on body weight and on surface area, are presented.

The correlation of hippuric acid excretion with these two measures of body size was almost identical in this series of tests.

A COMPARISON OF TECHNIQUES FOR THE DIFFERENTIAL COUNTING OF BONE MARROW CELLS (GUINEA PIG)

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THE variations in technique used by different workers in obtaining and preparing specimens of bone marrow add considerably to the uncertainties which feature in any evaluation of differential counts of marrow.   The techniques which have been employed in the preparation of specimens for counting may be classified into one of three general methods, namely, the use of fixed smears, of sections, and of supravital preparations.

The present work was planned for the purpose of comparison of the counts made by these three general methods when employed by the same individuals, and applied to the same marrow.   No technique was found for the preparation of fixed smears, however, which yielded as representative a distribution of the cells, caused as little trauma to them, and permitted as delicate cytologic definition as could be obtained by the supravital and section techniques.   For these reasons, the differential counts of fixed smears were obviously less dependable than those by the other methods, and after preliminary trials, counts by that technique were excluded from the experimental correlations.

Methods.   The guinea pig was selected as the experimental animal because of the similarity of its marrow to that of the human and the need of data concerning the normal proportions of its cells.   Fifteen males and 4 females were used.   They were kept in the animal room 3 to 25 days on a liberal diet consisting of oats, rabbit pellets (Ralston Purina Company) and daily rations of greens, with water available at all times.   They weighed 290 to 500 gm. at the time of sacrifice and were all in excellent condition.

When ready for study, both thighs were shaved, and the pig was then anesthetized lightly with ether.   Ten cc. of physiologic saline were immediately injected intraperitoneally, and 2 to 4 cc. of blood removed by cardiac puncture. During the next 10 to 15 minutes the anesthetic was maintained at the same level while the blood clotted and was centrifuged for the serum.   A lethal dose of ether was then administered, and while it was taking effect, or immediately after death, one femur was removed.   The bone was opened lengthwise by nipping with rongeurs with care not to compress the marrow.   Blocks of marrow, about 5 x 3 x 3 mm., were scooped out with a scalpel and immediately dropped in the fixative recommended by Kingsley.[16]   The other femur was then removed and opened in similar manner, and the marrow was aspirated into a 5 cc. syringe through a 20 gauge needle, both of which had been previously moistened with the guinea pig's serum.   It was frequently necessary to separate the marrow into smaller pieces so that it would go through the needle. This was done by moving the needle back and forth within the marrow cavity or by gently fragmenting a specimen of marrow with the needle.   A small amount of serum was drawn into the syringe after the marrow had been aspirated so that the final volume totaled 0.25 to 0.5 cc.   The syringe was

* Now on active service with the Armed Forces.

then vigorously shaken. The resultant suspension of tiny fragments of marrow in serum was used for the supravital preparations, and for the marrow serum mixtures employed in the preparation of fixed smears.

The methods which were tried in the preparation of the fixed smears were as follows: (1) Marrow touched to cover-slips. (2) Scrapings of marrow spread on cover-slips with a scalpel. (3) Marrow-serum mixtures (described above) pulled between two cover-slips. (4) Cover-slips flooded with the marrow-serum mixtures and allowed to dry. (5) Cover-slips flooded with the marrow-serum mixtures, and immediately fixed with absolute methyl alcohol. (6) Cover-slips flooded with the marrow-serum mixtures, followed by withdrawal of as much of the serum as possible by suction, and drying at an angle of 45 degrees.

With the exception of Method 5, the smears made by each of the above methods were dried in air and then immediately fixed in absolute methyl alcohol, as recommended by Kingsley. They were stored in cardboard boxes and stained within 3 weeks of preparation. Both Kingsley's[11] and Wright's stains were used. The latter was employed in the standard strength and also after dilution to 50% with absolute methyl alcohol. The time for staining was varied with the Kingsley's stain, as recommended,[16] and under those conditions that stain yielded the better results. Differentiation of the staining, as described for sections, was unsuccessful.

The fixed blocks were dehydrated and embedded according to the technique recommended by Kingsley. The sections were cut routinely at 3 micra and stained according to the procedure outlined by Kingsley. The counts were made from consecutive fields.

The slides and cover-slips for the supravital smears were cleaned and stained as described by Cunningham and Tompkins.[1] The neutral red dye was used in the proportion of 0.9 cc. of a saturated solution in absolute alcohol to 10 cc. of absolute alcohol. A drop of the marrow-serum mixture on a cover-slip was inverted on a stained slide and rimmed with salvoline in the manner employed in making supravital blood smears. Upon macroscopic examination of the smears, there could be seen small, separate fragments of marrow which varied in size from 2 mm. in diameter to particles which were barely discernible. Under the microscope, the cells around the periphery of the smaller fragments were thinly spread and well stained. The differential counts were made in those areas, not too far peripherally where cells had wandered from the fragment, or been floated centrifugally, and not too far centrally where they were too tightly packed for accurate detail. The number of cells that could be counted on the periphery of a single fragment varied with the size and thinness of the fragment. Occasionally only one fragment was necessary to obtain the desired number of cells (see below), but usually at least two, and frequently more, were used. The spreads were protected from direct sunlight and frequently allowed to remain at room temperature for 30 to 45 minutes before use. The cells remained in a perfectly satisfactory condition during that period of time. This technique differs from that described by Sabin in that intact fragments of marrow are examined, rather than freed cells

TABLE 1.—CHARACTERISTICS OF THE CELLS OF BONE MARROW

Cells	In sections (Kingsley's stain)						Stained supravitally (neutral red)					
	Shape	Cytoplasm		Nuclei			Cytoplasm			Nuclei		
		Color	Granules	Character	Shape	Nucleoli	Color	Granules	Vacuoles	Refractility	Shape	Nucleoli
Myeloblast	Round	Pale blue	0	Very vesicular	Round	Variable	Colorless	0	0	Unappreciable	Round	Variable
Myelocyte	Round	Paler blue	+ to ++++	Vesicular or reticular	Round or oval	Variable	Colorless	+ to ++++	0 to +	Unappreciable	Round or oval	Variable
Polymorphonuclear	Variable	Pale pink	++++	Reticular	Polymorphous	None	Colorless	++++	+ to ++	Slight	Polymorphous	None
Megaloblast	Round	Deep blue	0	Vesicular	Round	Usually 1	Pale straw	0	+	Unappreciable	Round	1
Erythroblast	Round	Slate or purple	0	Dense, cart-wheel	Round	Chromatin clumps	Straw	0	+	Slight	Round	None
Normoblast	Round	Pink	0	Pycnotic	Variable	None	Yellow	0	0 to +	Considerable	Round	None
Lymphocyte	Round	Medium blue	0	Dense, clumped	Round	Variable	Colorless	0	+ to ++	Considerable	Round	Variable
Monocyte	...	...	...	...	...	...	Colorless	0	++++	Slight	Variable	None
Chsmatocyte	...	...	...	...	...	...	Colorless	Variable	++++	Slight	Variable	Variable
Reticular cell	Elongated	Colorless	0	Very vesicular	Elongated	Variable	Colorless	0	+	Unappreciable	Oval	Variable

0 = none; + = rare; ++ = moderate number; +++ = many; ++++ = very many.

TABLE 2.—DIFFERENTIAL COUNTS BY P
(500 Cells Included in Each Co.

Cells	Ob-server	2 Sv	2 Sec	5 Sv	5 Sec	6 Sv	6 Sec	7 Sv	7 Sec	8 Sv	8 Sec	9 Sv	9 Sec	10 Sv	10 Sec	12 Sv	12 Sec	14
Myeloblasts	1	*4.6*	*10.8*	*2.1*	*5.2*	*7.2*		*8.8*		*5.0*		*4.4*		*2.9*		*8.1*	*2.1*	*1.9*
	2	4.0		4.4		2.8		4.2		5.2		5.0		3.0		1.0	3.6	17
Myelocytes	1	*29.0*	*13.6*	*27.1*	*9.6*	*15.4*		*8.1*		*10.0*		*29.2*		*16.1*		*7.3*	*10.0*	*8.2*
	2	23.2		26.8		36.6		10.2		27.8		29.0		28.4		30.2	20.0	37.3
P.M.N.	1	*16.0*	*30.5*	*35.8*	*40.1*	*37.6*		*28.3*		*29.9*		*15.8*		*26.3*	*15.6*	*21.0*	*13.0*	
	2	37.0		21.4		30.6		25.2		19.0		27.6		20.8	13.2	15.2	33	
Total myeloid cells	1	*49.6*	*55.9*	*65.0*	*54.9*	*60.2*		*39.7*		*44.9*		*49.5*		*45.8*	*26.3*	*33.1*	*22.5*	
	2	64.2		52.6		70.0		39.6		52.0		61.6		52.2		64.4	38.8	42.3
Megaloblasts	1	*2.6*	*3.8*	*1.8*	*3.6*	*2.0*		*4.1*		*1.8*		*1.6*		*1.9*		*2.2*	*3.3*	*2.0*
	2	2.0		2.4		2.0		3.2		4.8		3.6		2.2		1.2	5.2	31
Erythroblasts	1	*6.8*	*9.0*	*6.0*	*15.0*	*19.1*		*31.0*		*21.2*		*22.4*		*21.2*	*11.8*	*15.0*	*7.2*	
	2	12.2		11.8		5.0		15.4		9.0		13.4		18.0	5.6	16.2	10.1	
Normoblasts	1	*30.6*	*19.4*	*15.1*	*16.4*	*8.3*		*15.9*		*25.7*		*15.8*		*23.1*	*44.2*	*52.5*	*44.2*	
	2	12.0		16.8		7.0		19.4		19.2		11.6		15.6	20.6	23.2	29.4	
Total nucleated erythroid cells	1	*40.0*	*32.2*	*22.9*	*35.0*	*29.4*		*51.0*		*46.7*		*39.6*		*46.2*	*57.7*	*51.4*	*54.9*	
	2	26.2		31.0		14.0		38.0		33.0		28.6		35.8	27.4	41.6	42.6	
Total myeloid and nucleated erythroid cells	1	*89.6*	*88.1*	*87.9*	*89.9*	*89.6*		*90.7*		*91.6*		*89.0*		*91.5*	*84.0*	*84.5*	*77.4*	
	2	90.4		83.6		84.0		77.6		85.0		90.2		85.0	91.5	83.4	84.9	
M/E ratio	1	*1.2*	*1.7*	*2.8*	*1.6*	*2.0*		*0.8*		*1.0*		*1.2*		*1.0*		*0.5*	*0.6*	*0.4*
	2	2.5		1.7		5.0		1.0		1.6		2.2		1.5		2.3	0.9	1.0
Lymphocytes	1	*6.4*	*10.0*	*6.3*	*4.2*	*6.8*		*6.5*		*5.6*		*6.6*		*5.6*		*8.3*	*12.5*	*5.1*
	2	7.8		13.4		13.4		18.0		10.6		7.6		10.2		4.6	14.4	3.2
Monocytes	1	*3.4*		*3.5*												*4.7*		*11.9*
	2															0.6		1.96
Clasmatocytes	1	*0.2*		*0.3*												*1.4*		*1.1*
	2															0.8		0.6
Megakaryocytes	1	*0.3*	*1.4*	*1.7*	*1.2*	*0.4*		*1.0*		*0.8*		*1.0*		*1.6*		*1.0*	*0.4*	*1.4*
	2	1.5		1.2		1.6		1.2		1.2		1.4		0.2		2.2	0.4	1.5
Reticular cells	1	*0.0*	*0.0*	*0.0*	*4.2*	*3.0*		*1.8*		*1.8*		*3.2*		*1.5*		*0.0*	*2.4*	*0.7*
	2	0.0		1.8		1.0		3.2		3.2		0.8		1.6		0.0	1.6	0.1

* Figures in italics, means obtained by Observer 1.

counted 500 cells in each preparation, both supravital and section, with the result that 1000 cells were counted by each observer, or that 1000 cells were counted by each method. Krumbhaar and Custer[17] have determined that this number of cells is usually sufficient for dependable counts of marrow. The counting was kept strictly individual without interchange of opinion concerning cellular identity or reference to other counts of the same marrow, in order to insure as severe a test of the individual techniques as possible.

Techniques and Both Observers
(1000–2000 in Each Experiment)

	15 Sv.	Sec.	16 Sv.	Sec.	17 Sv.	Sec.	18 Sv.	Sec.	19 Sv.	Sec.	20 Sv.	Sec.	21 Sv.	Sec.	22 Sv.	Sec.	23 Sv.	Sec.	24 Sv.	Sec.	Mean by each observer Sv.	Sec.	Mean of all counts Sv.	Sec.
	1.4	4.0	4.0	4.2	4.1	3.6	3.4	2.2	3.2	1.0	2.0	2.1	2.6	3.1	1.8	2.6	1.8	3.0	1.6	2.0	2.7	3.9	2.8	4.0
	1.8	4.0	3.2	3.8	3.2	3.6	4.0	5.2	3.6	4.0	4.2	3.4	3.4	4.6	3.2	1.6	2.0	4.6	2.6	2.6	2.8	4.1		
	11.0	9.4	9.0	14.5	13.1	19.0	7.0	12.3	12.0	9.4	13.6	14.6	15.2	14.2	13.5	14.0	12.6	13.8	10.3	8.9	13.5	13.3	19.0	18.2
	17.0	16.4	31.2	17.0	24.0	27.4	17.6	30.8	18.4	23.8	28.4	18.6	19.6	39.6	16.2	18.0	12.0	12.6	21.0	19.4	24.4	23.1		
	19.1	32.3	17.9	35.4	18.2	28.8	20.1	37.7	15.5	41.3	27.4	34.1	28.7	37.0	31.1	35.2	29.2	40.8	24.0	19.5	22.3	31.3	16.9	27.7
	14.4	21.4	5.6	25.6	7.8	20.0	11.6	25.0	17.2	31.8	13.0	35.2	13.4	24.2	15.4	32.0	11.8	17.6	11.2	17.0	11.5	24.0		
	31.5	45.7	30.9	54.1	35.4	51.4	30.5	52.2	30.7	51.7	43.0	50.8	46.5	54.3	46.4	51.8	43.6	57.6	35.9	30.4	38.4	48.5	38.6	49.9
	33.2	41.8	40.0	46.4	35.0	51.0	33.2	61.0	39.2	59.6	45.6	57.2	36.4	68.4	34.8	51.6	25.8	34.8	34.8	39.0	38.7	51.2		
	2.0	2.0	2.2	2.2	2.0	1.0	1.8	1.6	2.2	2.4	1.8	1.2	1.7	2.1	2.2	1.4	1.2	1.0	0.6	2.5	1.9	2.3	2.4	3.0
	4.6	5.0	3.0	5.4	2.4	2.2	3.2	4.4	3.6	4.4	3.0	2.4	2.8	1.6	2.8	3.2	2.0	5.2	2.8	4.2	2.9	3.6		
	6.8	18.9	5.0	14.2	4.5	8.8	5.6	15.9	6.0	18.3	10.5	25.4	4.2	25.7	5.0	28.6	4.1	26.6	2.8	38.2	6.1	20.8	6.5	16.7
	9.2	9.4	6.8	8.6	7.0	8.8	7.0	7.0	4.8	7.2	4.4	5.2	6.6	6.6	6.2	8.8	7.8	21.4	5.8	25.0	6.8	12.5		
	31.9	21.5	32.3	20.1	26.2	25.2	26.0	25.0	29.9	18.7	25.6	12.7	21.6	9.4	17.7	9.2	27.4	8.4	19.0	15.1	25.0	18.0	26.6	17.3
	35.6	26.8	22.4	22.8	21.2	25.6	30.0	17.4	23.8	18.0	19.4	15.6	22.6	6.2	22.2	13.2	29.2	13.6	26.0	10.6	25.2	16.6		
	40.7	42.4	39.5	36.5	32.7	35.0	33.4	42.5	38.1	39.4	37.9	39.3	27.5	37.2	24.9	39.2	32.7	31.0	22.4	55.8	36.0	41.1	35.5	37.0
	49.4	41.2	32.2	36.8	30.6	36.6	40.2	28.8	32.2	29.6	26.8	23.2	32.0	14.4	31.2	25.2	39.0	40.2	34.6	39.8	34.9	32.8		
	72.2	88.1	70.4	90.6	68.1	86.4	63.9	94.7	68.8	91.1	80.9	90.1	74.0	91.5	71.3	91.0	76.3	88.6	58.3	86.2	74.4	89.6	74.0	86.8
	82.6	83.0	72.2	83.2	65.6	87.6	73.4	89.8	71.4	89.2	72.4	80.4	68.4	82.8	66.0	76.8	64.8	75.0	69.4	78.8	73.6	84.0		
	0.8	1.1	0.8	1.5	1.1	1.5	0.9	1.2	0.8	1.3	1.1	1.3	1.7	1.5	1.9	1.3	1.3	1.9	1.6	0.6	1.2	1.3	1.2	1.6
	0.7	1.0	1.2	1.3	1.1	1.4	0.8	2.1	1.2	2.0	1.7	2.5	1.1	4.7	1.1	2.0	0.7	0.9	1.0	1.0	1.2	1.9		
	11.0	10.0	15.3	7.0	8.8	8.8	12.3	2.6	12.4	5.9	10.1	6.2	7.2	5.6	14.5	5.2	9.5	6.8	22.4	9.9	10.7	6.9	11.3	10.2
	8.8	14.6	11.6	13.6	11.8	10.2	8.4	9.0	12.8	8.0	13.8	16.4	16.6	14.8	16.6	20.0	20.2	22.4	14.2	20.2	11.8	13.4		
	9.6		11.2		15.4		18.8		13.9		4.9		11.1		10.6		12.6		15.7		10.8		11.0	
	5.6		14.8		17.2		15.0		12.4		10.2		12.6		13.8		10.8		11.6		11.2			
	2.0		1.6		1.6		1.6		2.4		1.6		2.7		0.6		0.4		1.4		1.4		1.4	
	1.4		1.0		1.6		0.8		1.4		1.2		1.4		2.4		2.0		2.0		1.4			
	2.8	1.0	0.8	0.8	3.3	1.2	2.2	1.4	1.0	1.4	2.0	1.6	2.9	1.2	1.8	0.2	0.8	0.2	1.2	1.2	1.6	1.0	1.6	1.1
	1.6	1.6	0.4	1.8	2.6	1.2	1.4	0.8	1.2	1.2	1.8	1.4	0.8	1.0	1.2	0.8	1.4	0.6	2.2	0.2	1.5	1.1		
	2.4	1.0	0.4	1.4	2.2	3.8	1.2	1.0	0.8	1.4	0.6	2.2	1.8	1.5	1.0	3.2	0.4	4.2	0.4	2.5	0.8	2.4	0.7	1.9
	0.0	0.8	0.0	1.4	1.0	1.0	1.0	0.4	0.8	1.6	0.6	1.8	0.2	1.4	0.8	2.4	0.8	2.0	0.6	0.8	0.5	1.5		

The main morphologic criteria used in the identification of the cells by either technique are listed in Table 1. Differentiation of the younger cells in sections is inevitably dependent upon comparisons and evaluations relative to the staining of other cells in the same preparation, and there is no infallible way to differentiate individual early forms in stained preparations of bone marrow, if seen alone. This is achieved with considerable certainty, however, if the staining of any given section is considered as a whole.

It is recognized that the cytologic classification chosen is subject to controversy. It was chosen merely to facilitate comparison between the two techniques by synchronizing the nomenclature where possible, and no attempt is intended to uphold any specific concepts as to cellular origin. No attempt was made to separate either the myelocytes or polymorphonuclears into sub-groups.

Presentation and Discussion of the Experimental Data. Throughout the text the word "duplicate" is used to indicate two counts made by the same technique, but by different observers, on different specimens of the same marrow. The word "corresponding" is used to indicate two counts made by the supravital and section techniques, respectively, by the same observer on different specimens of the same marrow. The observers, and the counts by each, are referred to separately as the first and second, respectively.

The differential counts by each observer are listed in Table 2. Supravital counts were not made on animals 6 to 10 inclusive by Observer 1, and on animals 2 to 10 inclusive by Observer 2. Table 3[1] was compiled from Table 2 in order to facilitate evaluation of differences between counts. As defined in this table, a difference between counts is "statistically significant" if the "probability" of its occurrence by chance is less than once in 100 times.

The data may now be considered from the following aspects:

1. *The Variations Between "Duplicate" Counts by Different Observers Using a Single Technique (Tables 2 and 3).* This analysis is designed to determine the extent of personal differences in classification, irrespective of technique, and the degree to which susceptibility to such personal differences is influenced by technique.

TABLE 3.—MEAN "DUPLICATE" AND "CORRESPONDING" COUNTS, AND THE PROBABILITY* OF THE OCCURRENCE OF THE DIFFERENCES BETWEEN THESE MEANS†

	"Duplicate" counts (i. e., same technique, 2 observers)						"Corresponding" counts (i. e., 2 techniques, same observer)					
	Supravital			Sections			Observer No. 1			Observer No. 2		
	Mean			Mean			Mean			Mean		
Type of cell	Obs. 1	Obs. 2	Prob-ability	Obs. 1	Obs. 2	Prob-ability	Sv.	Sect.	Prob-ability	Sv.	Sect.	Prob-ability
Myeloblasts	2.7	2.8	0.81	3.9	4.1	0.87	2.7	3.9	0.06	2.8	4.1	<0.01
Myelocytes	13.5	21.4	<0.01	13.3	23.1	<0.01	13.5	13.3	0.92	21.4	23.1	0.72
Polymorphonuclears	22.3	11.5	<0.01	31.3	24.0	<0.01	22.3	31.3	<0.01	11.5	24.0	<0.01
Sum	38.4	35.7	0.94	48.5	51.2	0.40	38.4	48.5	<0.01	35.7	51.2	<0.01
Meta(?)blasts	1.9	2.9	<0.01	2.3	3.6	<0.01	1.9	2.3	0.17	2.9	3.6	0.11
Erythroblasts	6.1	6.8	0.49	21.8	12.5	<0.01	6.1	21.8	<0.01	6.8	12.5	<0.01
Normoblasts	25.0	25.2	0.33	15.0	16.6	0.51	25.0	15.0	<0.01	25.2	16.6	<0.01
Sum	35.0	34.9	0.75	41.1	32.8	<0.01	35.0	41.1	0.10	34.9	32.8	0.31
Lymphocytes	13.7	11.8	0.36	6.9	13.4	<0.01	13.7	6.9	<0.01	11.8	13.4	0.35
Monocytes	1.8	11.2	0.64	.			13.8			11.2		
Plasma cytes	1.4	1.4	0.92				1.4			1.4		
Megakaryocytes	1.6	1.5	0.72	1.0	1.1	0.31	1.6	1.0	<0.01	1.5	1.1	0.61
Reticular cells	0.8	0.3	0.21	2.4	1.5	<0.01	0.8	2.4	<0.01	0.3	1.5	<0.01

* This probability is a measure of how often the observed differences might be equalled or exceeded by chance. When the probability is less than 0.01, i. e., once in 100, the difference is termed to be "statistically significant"; if it is likely to occur as a matter of chance. Values obtained from Fisher's table of values (1).

† These mean values are derived from Table 2.

It is obvious from Table 3 that there is less variation between the duplicate supravital counts than between the duplicate section counts. In fact, with the exception of the myelocytes, polymorphonuclears and megaloblasts, the differences between the means of the duplicate supravital counts are not "statistically significant," while those between the means of the duplicate section counts are "significant" in most instances. Further analysis of the table shows that while the deviations between the means of the duplicate counts of myelocytes and polymorphonuclears are "significant," by either technique, the deviation between the means of the duplicate counts of total myeloid cells is "insignificant" in the supravital counts, and relatively "insignificant" in the fixed counts. The variations between the duplicate counts of myelocytes and polymorphonuclears must, therefore, be dependent largely upon "personal factors" (chiefly upon lack of agreement on the part of the two counters in differentiation between the members of the myeloid series) and not upon the limitations of the methods employed. This is borne out by the fact that the differences between the duplicate counts of these cells occur in a single direction in practically all counts (Table 2).

The same conclusion applies to the differences between the duplicate counts of megaloblasts by either method, since they also occur almost uniformly in one direction (Table 2).

Analysis of the differences between the duplicate section counts of the remaining cells of the marrow indicates that they also are dependent largely upon personal differences in cytologic differentiation. The differences between the duplicate section counts of erythroblasts are almost consistently in one direction (Table 2), but, unlike the myeloid series, they are not counterbalanced by the other members of the erythroid series and therefore the means of the total erythroid counts also differ "significantly" (Table 3). The differences between the duplicate section counts of erythroblasts occur almost uniformly in the opposite direction to the differences between the duplicate counts of lymphocytes and are of the same order of magnitude (Table 2). It seems probable, therefore, that lack of agreement on the part of the two counters in differentiation between these two types of cells in sections represents the "personal factor" responsible for the variations in the duplicate section counts of not only erythroblasts and lymphocytes, but of all the other values dependent upon them (total nucleated red cells, combined myeloid and erythroid cells, and M/E ratios).

This analysis, therefore, indicates that when "statistically significant" differences occur by either technique between duplicate counts by different individuals they are the result of differences in cytologic differentiations by the individuals, and are therefore controllable. Such "personal differences" apparently occur more easily with the section technique.

2. *Comparison Between "Corresponding" Supravital and Section Counts by a Single Observer (Tables 2 and 3).* This analysis is designed to bring out points of difference in counts made by the same individual

by the two methods, the reasons for difference, and the relative dependability of counts by each technique.

From Table 3 it is seen that, with the exception of the lymphocytes, the differences which occur between corresponding counts by the two methods are in the same direction for each observer and may, therefore, be regarded as due to differences of technique and not to "personal factors." These differences are discussed in groupings based on probable interrelationships.

The percentages of both myeloblasts and, to less extent, megaloblasts tend to be slightly greater in the section counts (Table 2). The percentage of erythroblasts is greater, and that of normoblasts less in the section counts, although the total percentage of nucleated red cells is usually the same by either method. These three facts, as well as the irregularities in the "duplicate" lymphocytic counts, all seem to be explainable on the same basis. In supravital preparations, differentiation of the erythroid series depends upon the quantity of hemoglobin detectable in the unstained living cell; in sections, differentiation of cellular types depends upon the character of the nuclei and the degree of basophilia of the cytoplasm, coupled with the presence or absence of cytoplasmic inclusions. The delicacy of detection of these factors in sections is dependent upon the extent of crowding of the cells and upon the depth and differentiation of staining. The less complete the differentiation, the more pronounced becomes the basophilic side of the picture, i. e., density of nucleus and blueness of cytoplasm, and the less the acidophilic side, i. e., granules and hemoglobin. Consequently there is a tendency toward overshadowing of the earliest acidophilic characteristics in fixed staining with the result of an apparently slightly increased proportion of the youngest cells in section counts. For the same reason there is an apparent shift between erythroblasts and normoblasts in favor of the former. Finally, the shift toward basophilia causes difficulty in the differentiation between lymphocytes and erythroblasts. It is probable that this is the factor involved in the lack of agreement between the "duplicate" counts of these cells which was discussed previously. The fact that the difference between the means of the "corresponding" counts of lymphocytes is reversed for the two observers (Table 3) may reflect greater difficulty for one of them in differentiation between these cells in sections.

The percentages of polymorphonuclears are consistently higher in the section counts, while the percentages of myelocytes are relatively the same in both counts. Consequently, the percentages of total granulocytes are proportionately higher in the section counts, and therefore also the combined total percentages of erythroid and myeloid cells, and the M E ratios.

There are two factors which should be considered as possible explanations of this difference in polymorphonuclear counts by the two methods. First, the manner of making the supravital counts was such that the more motile and more easily disturbed polymorphonuclears might have been floated peripherally from the fragments of marrow upon which the counts were made, and thus have been excluded from

the counts. Since the divergence of the supravital counts from the fixed counts is so constant, this explanation seems unlikely, as floating of the same proportion of cells in every smear would hardly be expected. Second, the average increase in the polymorphonuclears in the section counts (10.8%) is practically equal to the mean percentage of monocytes in the supravital counts (11%). Monocytes are recorded only in the latter counts. The nuclei of monocytes are frequently similar to those of the younger polymorphonuclears. Both cells have cytoplasmic granules in fixed material, and the cytoplasm itself is frequently indiscernible in crowded areas. For these reasons it is probable that inclusion of monocytes with polymorphonuclears accounts for the consistently greater proportion of polymorphonuclears by the section technique.

The percentage of reticular cells is greater in the section counts (Table 2), the average increase (1.3%) being equal to the percentage of clasmatocytes in the supravital counts (1.4%). As in the case of monocytes, clasmatocytes are recorded only in the latter counts. Reticular cells and clasmatocytes generally assume a similar elongated shape. Their nuclei are fairly similar and their cytoplasm equally indefinable unless characterized by inclusions. From these various considerations, therefore, it seems probable that the increase in reticular cells in the fixed counts is due to inclusion of clasmatocytes with counts of reticular cells.

3. *The Marrow of the Normal Guinea Pig* (based on the average of the combined counts by both observers. Last column, Table 2). Seventy-five per cent of the cells in supravital counts of the marrow of normal guinea pigs, and 85% in fixed counts, are comprised of the combined myeloid and erythroid cells. Lymphocytes comprise roughly 10% by either method, and the sum of the reticular cells, clasmatocytes and giant cells, 5%. Finally, monocytes comprise 10% in supravital counts while their inclusion with polymorphonuclears in section counts, as has been discussed, is probably responsible for the higher value of the sum of the myeloid and erythroid cells in the section counts.

The percentages of both myeloblasts and megaloblasts are slightly greater in section than in supravital counts. By either method alone, however, they equal each other and are less than the percentage of any other cells of their respective series.

There was considerable discrepancy on the part of the two counters in differentiation between myelocytes and polymorphonuclears, respectively, as has been discussed under heading "1." Therefore, although the average combined percentage of myelocytes by either method is the same, the discrepancy in classification makes it impossible to formulate any statement concerning the normal proportion of myelocytes to polymorphonuclear cells.

The ratio of normoblasts to erythroblasts varies with the technique, although the total number of cells of the erythroid series is uninvolved. In the supravital counts there are four times as many normoblasts as erythroblasts. In the section counts, the per cent of normoblasts is less than that of erythroblasts. That the anesthesia may have influ-

enced the erythroid values is possible, but not very probable, in view of the short period in which it was in effect before the specimens were obtained.

While slightly higher by the section than by the supravital technique, the M/E ratios fluctuate around unity. This figure is low compared to the ratios obtained by other workers with other species, as reviewed by Sabin.[22] The fact that the M/E ratio represents the proportion of all myeloid cells (mature polymorphonuclears ready for emigration as well as immature myelocytes) to only the immature nucleated red cells, irrespective of the number of possibly newly formed erythrocytes, seems to throw question upon the wisdom of too rigid an interpretation or comparison of this value.

Discussion. Isaac's[9] observation that the cells of marrow stain more intensely and more like blood cells when exposed to serum is significant in evaluation of techniques for the study of marrow. He found[10] that the morphology of cells prepared by the touch technique differs from that of blood cells evidently for lack of suitable moistening. With this exception, mixture with more or less serum obviously occurs with most of the techniques used for the preparation of smears of marrow.

Custer,[2] Tuohy and Gillespie,[23] Dameshek,[3] Jones,[11] Kato,[13] Krumbhaar and Custer,[17] and Gall,[8] as well as others, obtained satisfactory cytologic detail with fixed smears prepared by either smearing marrow on slides or by the touch technique. The latter 3, however, believe that differential counts made by these techniques are inaccurate, and that, as Peabody[19] first suggested, study of sections is more dependable for estimations of relative cellularity. Morris and Falconer,[18] on the other hand, compared smear preparations of aspirated marrow to sections and state that "smears and sections checked well." They are not specific, however, as to whether reference is had to qualitative or quantitative comparisons.

Sabin, Miller, Smithburn and Hummel[21] made duplicate counts of rabbits' marrow from fixed and supravital films and obtained good correlation in half of the instances. In their opinion the supravital technique is the better standard. Doan and Zerfas[5] used both methods with satisfaction. Gall[8] found the supravital, as well as the touch technique, unsatisfactory for counts. Jones[12] agrees in regard to the former technique, but not in regard to the latter.

Custer,[2] as well as Dameshek, Henstell and Valentine[4] and Doan,[6] suggest that adequate study of the marrow should include more than one technique. Krumbhaar and Custer[17] suggest, further, that comparative counts should be made, not only by the same techniques, but by the same person. The concluding words of Doan and Zerfas[5] in their enumeration of the factors which give rise to this variety of opinions concerning techniques are illustrative of the status up to the present time: ". . . . all of these, and more, make it necessary to be very conservative in the drawing of deductions from any one limited series of observations or in trying to compare the figures obtained from different investigators."

In the studies reported here, a variable degree of trauma and inade-

quate distribution were found to be inevitable in fixed smears of marrow, and consequently to invalidate differential counts made from them. Detailed comparison between differential counts by different methods was therefore carried out only on counts from sections, and from small pieces of marrow stained supravitally. From the consideration of the data it seems apparent that fairly dependable differential counts of marrow are possible by either of these techniques. There are certain differences in counts by the two methods, however, which are inherent in the techniques and which must be recognized and given due evaluation.

The supravital technique permits of closer agreement between duplicate counts and of surer differentiation of all types of cells. It permits the detection of the two phagocytic mononuclear cells, clasmatocytes and monocytes, and it facilitates the study of certain of the physiologic activities of marrow cells. On the other hand, it permits study of only the hematopoietically active areas of the marrow, and gives little information concerning the frequency of such areas.

The section technique permits of sufficiently close agreement between duplicate differential counts for most purposes, and offers the advantage of a general survey of the marrow as a whole, hematopoietic centers as well as inactive ones. It does not permit of differentiation of the phagocytic mononuclear cells, which obviously results in a corresponding inaccuracy elsewhere (probably in the counts of polymorphonuclear and reticular cells).

There are various technical factors in the preparation of sections for counting which require great care if the maximum accuracy is to be obtained. If these are neglected the sections may actually mislead, since errors in technique may cause incorrect classification of cells. Meticulous adherence to the proportions stipulated by Kingsley[16] for the fixative has been found to be perhaps the most important factor involved. A mistake at that stage is irrevocable and can lead to subtle errors in classification that are extremely difficult to detect. Most important among these is a granular precipitation of hemoglobin which results in confusion between nucleated red cells and granulocytes.

Inadequate staining may also lead to errors in differentiation, but they are rectifiable by use of new sections. Experience with the stain and the degree of differentiation necessary for accurate differential counting are all that are needed to avoid such errors and they will therefore not be discussed in minutiae.

We agree with those who advocate that examination of marrow should include the use of more than one technique. However, where that is impracticable, relatively dependable differential counts may be made by either of the techniques employed in these studies; but those by the supravital technique are subject to less error, and offer more information. Conclusions based upon the counts made with either technique must be made with cognizance of the sources of error in each, and especially with full appreciation of the fact that a differential count of small portions of marrow represents the relationship between cells in active hematopoietic areas, and does not necessarily offer information as to the relative frequency of such areas.

Summary. 1. A method is described for counting the hematopoietic cells of small pieces of bone marrow supravitally.

2. Counts of bone marrow of normal guinea pigs have been made from (1) fixed smears prepared by a variety of methods; (2) small pieces of marrow stained supravitally; and (3) sections fixed and stained by Kingsley's method.

3. Inadequate distribution and trauma are found to be inherent sources of error in the use of fixed smears. Differential counts made from them are therefore less dependable than by the other two methods. The data by the other two methods have been analyzed statistically.

4. The difference between section counts of the same marrow by different observers is greater than between supravital counts under the same conditions. Both methods, however, are sufficiently reliable for studies based upon comparative, rather than absolute, values.

5. There are certain differences between counts of the same marrow by the section and supravital techniques, respectively, which must be taken into consideration in evaluation of any count of bone marrow. These are inherent in the techniques and have been analyzed for the probable explanation. The most important differences between section and supravital counts are: (1) a greater percentage of polymorphonuclear cells in section counts; (2) inability to differentiate monocytes and clasmatocytes, specifically, in section counts; and (3) a shift toward the younger cells of any series in section counts. The method used in any study, therefore, should always be stated.

6. The mean differential count of the bone marrow of normal guinea pigs is established, and certain generalizations concerning the proportional relationships are formulated from it.

REFERENCES

1. CUNNINGHAM, R. S., and TOMPKINS, E. H.: Handb. of Hematology, 1, 553, 1938.
2. CUSTER, R. P.: Am. J. Med. Sci., 185, 617, 1933.
3. DAMESHEK, W.: Am. J. Med. Sci., 190, 617, 1935.
4. DAMESHEK, W., HENSTELL, H. H., and VALENTINE, E. H.: Ann. Int. Med., 11, 801, 1937.
5. DOAN, C. A., and ZERFAS, L. G.: J. Exp. Med., 46, 511, 1927.
6. DOAN, C. A.: Handb. of Hematology, 3, 1839, 1938.
7. FISHER, R. A.: Statistical Methods for Research Workers, Oliver & Boyd, London, pp. 307, 1932.
8. GALL, E. A.: Am. J. Path., 13, 575, 1937.
9. ISAACS, R.: Science, 68, 547, 1928.
10. ISAACS, R.: Folia haematol., 40, 395, 1930.
11. JONES, O. P.: Arch. Int. Med., 60, 1002, 1937.
12. JONES, O. P.: Handb. of Hematology, 3, 2013, 1938.
13. KATO, K.: Am. J. Dis. Child., 54, 209, 1937.
14. KINGSLEY, D. M.: Stain Technology, 10, 127, 1935.
15. KINGSLEY, D. M.: J. Lab. and Clin. Med., 22, 524, 1937.
16. KINGSLEY, D. M.: Folia haematol., 57, 87, 1937.
17. KRUMBHAAR, E. B., and CUSTER, R. P.: Am. J. Med. Sci., 189, 630, 1935.
18. MORRIS, L. M., and FALCONER, E. H.: Arch. Int. Med., 30, 485, 1922.
19. PRATT, F. W.: Am. J. Path., 3, 179, 1927.
20. SABIN, F.: Phys. Rev., 8, 191, 1928.
21. SABIN, F. R., MILLER, F. R., SMITHBURN, R. M., and HUMMEL, L. E.: J. Exp. Med., 64, 97, 1936.
22. SABIN, F. R., and MILLER, F. R.: Har. B. of Hematology, 3, 1749, 1938.
23. TERRY, E. L., and GITTINGER, M. G.: J. Am. Med. Assn., 104, 1104, 1935.

PROGRESS

OF

MEDICAL SCIENCE

OPHTHALMOLOGY

UNDER THE CHARGE OF

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TOXIC EFFECTS OF SULFONAMIDES ON THE EYES

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With the main purpose of estimating the probable efficacy of various sulfonamides in the treatment of extra- and intraocular infections, a number of investigators have made determinations of the penetration of these drugs into the tissues of the eye. The relative concentration in the different tissues and fluids may have some bearing on the toxic as well as on the curative effects.

Bellows and Chinn[4,5] found that, in dogs, after a single massive dose of sulfanilamide by mouth (0.2 gm. per kilo of body weight), traces of the drug could be detected in the eye within 15 minutes. Maximum concentration was reached within 6 hours in all the tissues examined except the lens in which maximum concentration occurred in 12 hours. The concentration of sulfanilamide was found to be in the chorioretinal tissue 80%, in the corneo-scleral tissue 65%, in the aqueous 60%, in the lens 50%, and in the vitreous 45% of the concentration in the blood which reached 19.1 mg. per 100 cc. Elimination of the drug from the lens and vitreous was relatively slow so that at the end of 24 hours, the concentration in these tissues was about 120% of that in the blood. When divided therapeutic doses were given, the relative concentrations were essentially the same as after a single massive dose in the aqueous, vitreous and chorioretinal tissues but were definitely higher in the lens and corneo-sclera, 100% and 150% of the blood levels respectively. The concentration in the aqueous was not increased by the local application of heat, dionine, atropine or eserene but was increased by the instillation of mecholyl and by paracentesis, both of which increased the amount of protein in the aqueous probably by increasing the permeability of the capillaries in the ciliary body. In 2 patients who were taking 3 gm. of sulfanilamide by mouth daily 0.8 mg. per 100 cc. and 1.5 mg. per 100 cc. were found in the tears. Bellows and Chinn[4,5] were of the opinion that the drug passes into the tissues by simple diffusion and the tissues do not act to concentrate the drug. The sulfanilamide passes into the aqueous and vitreous by dialysis from the blood and

enters the lens from the surrounding media. Mengel[20] found a concentration of 1.5 to 3.2 mg. per 100 cc. in the aqueous and vitreous of 2 blind human eyes after the administration of sulfanilamide orally.

Meyer, Block and Chamberlain[21] found that, after the administration of 1.2 gm. of sulfapyridine by mouth to rabbits, the concentration in 4½ hours was in the blood 20 mg. per 100 cc., in the aqueous 14 mg. per 100 cc., and in the cornea 8.5 mg. per 100 cc. After 7½ hours the concentration was in the blood 10 mg. per 100 cc., in the aqueous 7.6 mg. per 100 cc., and in the cornea 15.7 mg. per 100 cc. Bellows and Chinn[4,5] found that 4 hours after the administration to dogs of 0.2 gm. of sulfapyridine per kilo of body weight the blood concentration was 6.1 mg. per 100 cc. The concentration in the sclera was 114%, in the cornea 110%, in the chorioretina 100%, in the vitreous 96%, in the aqueous 80%, and in the lens 18% of the blood concentration.

Bellows and Chinn[4,5] made determinations also of the amount of sulfathiazole in the tissues of the eye in dogs 4 hours after the administration of 0.2 gm. per kilo of body weight. They found that the concentration in the blood was 7.4 mg. per 100 cc. and that the concentration in the sclera was 140%, in the chorioretina 66%, in the cornea 27%, in the vitreous 13%, in the aqueous 5.2%, and in the lens 0% of that in the blood.

Scheie and Souders[27] made a comparison of the concentration of sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine in the aqueous after a single massive dose orally. In 6 hours the aqueous contained 72% of the blood level of sulfanilamide, 62.8% of sulfapyridine, 48% of sulfadiazine, and 17% of sulfathiazole. In 24 hours, the aqueous contained 78% of the blood level of sulfanilamide, 81% of sulfapyridine, 75% of sulfadiazine, and 18% of sulfathiazole. The secondary aqueous after paracentesis contained 80% of the blood level of sulfanilamide, 88% of sulfapyridine, 80% of sulfadiazine, and 59% of sulfathiazole. Scheie and Leopold[25] found that in eyes with experimentally produced corneal ulcers the concentration of sulfathiazole in the aqueous rose to 46% of that in the blood and in eyes with experimental infections in the vitreous to from 82% to 91% of the blood level. Also the local instillation into the eyes of mecholyl or histamine caused a rise in the aqueous to from 30% to 50% of the blood concentration. Liebman and Newman[18] obtained comparable results from a similar investigation. In the primary aqueous the concentration of sulfanilamide was 67% of that in the blood, of sulfapyridine 64%, of sulfadiazine 55%, and of sulfathiazole 17%. In the secondary aqueous the concentration of sulfanilamide in the aqueous was 96% of that in the blood, of sulfapyridine 98%, of sulfadiazine 102%, and of sulfathiazole 41%. Liebman and Newman[18] stated that analysis of the eyes obtained at necropsy from 2 patients who had received sulfapyridine and 2 who had received sulfathiazole yielded results similar to those obtained in rabbits' eyes.

Alvaro[1] stated: "The fact that sulfonamide compounds penetrate into the tissues of the eye in concentrations only somewhat lower than the concentration in the blood, and the demonstration of the potential absorption by the several parts of the eyeball, make it easy to understand why there is a comparatively large group of ocular changes which have been attributed to these drugs." Among the toxic manifestations which are reported to have occurred in the eyes, Alvaro[1] mentioned edema of the lids and conjunctiva, conjunctivitis, scleral reactions, cells in the aqueous, iritis, cataract formation, mydriasis, hemorrhagic extravasations in the retina, edema of the retina, optic neuritis, reduction in the fields of vision,

blurred vision of undetermined etiology, and transient changes in refraction. To these may be added the partial paralysis of the oculomotor nerve which was reported by Pitter[23] to have occurred during sulfanilamide therapy of gonorrhea. It is of interest to note, however, that with the exception of transient changes in refraction, reports of toxic manifestations in the eyes have been very infrequent. It seems probable that the relative infrequency of reports of the occurrence of conjunctivitis is due to the minor nature of the lesion and to its usual association with toxic lesions of the skin.

All of the changes in refraction reported to date have been in the direction of myopia except in the case described by Thorne[31] in which vision was improved from 20/200 to 20/20 in each eye by +3.50S and +.50Cyl ax 180. Since Thorne[31] suggested that the change in refraction might be due to spasm of the ciliary muscle, one wonders whether the minus sign may not have been inadvertently changed to plus in transcription. So far there has not been a very satisfactory explanation of the mode of development of these transient changes in refraction. The theory of spasm of the accommodation seems to have been pretty well disproved. The explanation of the myopia on the basis of edema of the lens, probably allergic or angioneurotic in origin, has been advocated by Spellberg,[30] Mattsson,[19] Gailey,[13] Bristow,[9] Rittenhouse,[25] Spearman,[29] Hornbogen,[17] and Blankstein.[6] Rittenhouse[25] has suggested the possibility that rapid absorption of the drug may bring about a change in water and salt metabolism which would affect the lens. He suggested also a possible toxic irritation of the parasympathetic fibers of the ciliary muscle. According to Rittenhouse,[25] Nitti and Bovet and Hageman and Blake were not able to produce sensitivity to sulfanilamide under experimental conditions. Blankstein[6] suggested that the edema of the lens might be the result of an osmotic change produced by the unequal distribution of the drug in the various tissues of the eye. Krause suggested, according to Blankstein,[6] that a low hydrogen ion content of the blood, which occurs at times during sulfonamide therapy, might activate the osmotic power of the lens tissue and favor its swelling.

Alvaro[1] collected 36 cases of transient myopia. Of these, 33 occurred during the course of sulfanilamide therapy and 3 during treatment with sulfapyridine. The amount of myopia developed in the sulfanilamide cases varied from 1.50 D to 4.50 D and averaged 2.60 D. In the 3 sulfapyridine cases, it was 2.00 D, 6.50 D, and 7.00 D, averaging 5.25 D. The amount was often different in the two eyes but both eyes were affected always. Men were affected slightly more often than women. The age incidence was as follows: below 20, 9.5%; between 20 and 30, 38.1%; between 30 and 40, 23.8%; and over 40, 28.6%. The smallest amount of sulfanilamide which had been taken before the onset of myopia was 0.3 gm. and the largest 42 gm. The smallest amount of sulfapyridine was 5 gm., and the largest 85 gm.; 36.36% of the individuals had taken less than 2 gm. of the drug; 13.6% between 2 and 4 gm.; 13.7% between 4 and 10 gm.; 22.6% between 10 and 20 gm.; and 13.7% more than 20 gm. The time of onset of the myopia after starting sulfanilamide varied from 12 hours to 14 days and in the sulfapyridine from 14 to 30 days; 36.36% of the cases occurred within 24 hours after the drug was started; 13.6% between the 1st and 4th days; 4.5% between the 4th and 9th days; 18.1% between the 10th and 20th days; and 22.7% after the 20th day. In 8 cases the myopia occurred after the drug had been stopped and started again in a second course. In only 1 of these cases had the drug been stopped because of the appearance of general signs of intolerance. There seemed to be

some relationship between the amount of myopia developed and the amount of the drug taken, the duration of treatment, and the age of the patient. Patients who had taken up to 2 gm. of the drug developed an average of 2.00 D of myopia; between 2 and 10 gm. 3.37 D, and over 10 gm. 4.17 D. Patients who had taken the drug for 24 hours or less developed an average of 2.00 D of myopia; between 2 and 5 days 3.16 D, between 6 and 15 days 4.60 D, and over 15 days 6.50 D. Patients below the age of 20 developed an average of 5.00 D of myopia; between the ages of 20 and 30, 4.29 D; between 30 and 40, 2.58 D; and over 40, 2.40 D. The myopia lasted for from 1 to 15 days (averaging 4.9 days). No relationship could be established between the amount of the drug taken and the duration of the myopia. All of the patients recovered without sequelæ.

With the exception of the cases reported by Hornbogen[17] and by Esterman[11] in which edema of the lids and conjunctivæ accompanied transitory myopia occurring in the course of sulfanilamide therapy, all the toxic conjunctival and scleral reactions have been described in cases under treatment with sulfathiazole.* Haviland and Long[16] reported that in 6 of 78 cases receiving sulfathiazole, there occurred between the 4th and 16th day of treatment conjunctival and scleral injection, restricted in the main to the exposed portions of the bulbar conjunctiva and sclera with burning and watery discharge. In 4 of the 6 cases the eye lesions occurred in association with skin lesions. In 3 cases the eye nearest the light was involved solely or primarily. The palpebral conjunctiva was involved also in the 2 cases most exposed to light. However, there was no "after sensitivity" to light and no recrudescence on exposure to light after discontinuance of the sulfathiazole. Exposure to light did not invariably bring on the conjunctivitis. No definite relationship could be established between the onset of the conjunctival reaction and the blood level of the drug. In 1 patient the conjunctival reaction recurred on readministration of the drug. Volini, Levitt, and O'Neil[24] reported that conjunctival reactions occurred in 5 of 180 patients receiving sulfathiazole, in 4 in association with skin reactions. The average dose taken by the affected patients was 34 gm., and the concentration of sulfathiazole in the blood averaged 4.2 mg. per 100 cc., varying from 2.5 to 7.1 mg. per 100 cc. The conjunctivitis was severe frequently with bright red injection of the palpebral and bulbar conjunctiva, edema of the eyelids, photophobia and seropurulent discharge. It cleared up rapidly without residuals after the drug was stopped. Volini[24] thought that immediate discontinuance was indicated on the appearance of the conjunctival reaction. Turkell and Wilhelm[22] observed 7 cases of conjunctivitis during administration of sulfathiazole. Quantitative determination of the sulfathiazole concentration in the tears was made in 4 of these 7 and in 10 other patients receiving sulfathiazole but without conjunctivitis. Sulfathiazole was found in the tears of all 14 in concentrations varying from 0.1 to 0.98 mg. per 100 cc. But the amount in the tears was not proportional to the blood concentration but was influenced by the secretory function of the lacrimal gland. In all cases of conjunctivitis, the sulfathiazole concentration in the tears reached 0.6 mg. per 100 cc. or more. However, in 6 of 10 cases without conjunctivitis, the sulfathiazole concentration was 0.56 mg. per 100 cc. or more. The conjunctivitis was not caused apparently by an increased concentration of sulfathiazole in the tears. According to Turkell and Wilhelm[22] "The conjunctivitis occurring during the administration of sulfathiazole is, in all likelihood, a reaction peculiar to the drug. Although sulfanilamide has been found in the tears in greater concentration than

* See footnote of O. Nagy reference on p. 263.

sulfathiazole, conjunctivitis has not been observed." Nor has it been reported during the administration of sulfapyridine. Four of the 7 patients had no conjunctivitis during the first course of therapy. The fact that conjunctivitis occurred during the second or a subsequent course of treatment suggested sensitization to the drug. The conjunctivitis cleared up in 1 to 4 days after discontinuance of the drug without serious sequelæ. Turkell and Wilhelm[32] regarded the development of conjunctivitis as an indication for stopping the drug. However, in 1 case, the drug was not stopped and the conjunctivitis cleared up in 4 days under treatment with zinc sulfate. The author has observed several cases similar to those described by Haviland and Long.[16]

Morrison[22] reported the development of an allergic edema and inflammation of the lids and conjunctiva which developed during the treatment of a chronic catarrhal conjunctivitis with a 5% sodium sulfathiazole ointment in lanolin petrolatum. The eyes were well 5 days after the drug was stopped. The edema recurred in one eye when the drug was reapplied to that eye only while the ointment base alone was applied to the other eye.

Four cases of acute optic neuritis have been reported in patients under treatment with sulfonamide compounds. Bucy[10] described reduction of vision to 6/200 with the right eye and 4/200 with the left eye with relative central scotomas and some blurring of the disk margins in a 16 year old girl who had received 14.4 gm. of sulfanilamide for chronic recurrent osteomyelitis with some other evidences of intolerance to the drug. The vision cleared up in 2 days after stopping the drug. Alvaro[1] records also (1) a case described by Valdeavellano,[33] a girl aged 18, who showed blurring of the vision with slight changes in the optic disks after receiving sulfanilamide orally and parenterally for 12 days and who recovered normal vision in a few days after stopping the drug; (2) a case described by Guerra,[15] a man who had received 17 gm. of some drug of the sulfanilamide group for gonorrhea. He was completely blind with dilated pupils, blurred optic disks and dilated congested retinal veins. Twenty-seven days after the drug was discontinued, vision was 20/30 in each eye; but the fields of vision were still contracted and the light sense and color sense were below normal; (3) a case observed by Bresser,[8] a man, aged 19, who had received 8 gm. of sulfapyridine in a period of 3 days. He had blurred vision without refractive error and with ophthalmoscopic evidences of optic neuritis. The vision was 20/20 in each eye 17 days after the drug was discontinued. A case which belongs probably in the same general category was reported by Bloom, Leech and Shaw.[7] A man, aged 26, had received 22 gm. of sulfathiazole in 84 hours. His vision was reduced suddenly to the ability to see hand movements at 6 inches. Ophthalmoscopic examination revealed tortuosity and dilatation of the retinal vessels especially the veins, small petechial hemorrhages, and multiple small white crystal-like spots throughout the retina but concentrated especially around the macula. The sulfathiazole concentration in the blood was 1 mg. per 100 cc. The patient was placed on a milk diet and was given intravenous glucose in distilled water, citrocarbonate, vitamin B complex, vitamin K, and calcium gluconate. The vision returned to normal in 12 days. It seems possible that this may have been some form of angiospastic retinitis since the blood pressure rose with the onset of the loss of vision to from 174/90 to 178/120. One week later it was 128/88 and in another week was 110/68. The patient was under treatment for cystitis, pyelitis, and renal colic. Only two reports have appeared in the literature of hemorrhagic extravasations into the retina in the course of sulfonamide therapy. The author

has observed several cases of this type in patients at the Mayo Clinic. Unfortunately no record was kept of the particular drug used in the individual cases. The hemorrhagic areas were of the thick so-called "purpuric" type. Baker[3] reported the case of a man, aged 36, who received 370 gr. of sulfanilamide in 4 days for the treatment of pyelitis with ureteral calculi. Vision was reduced to 20/60 in each eye. Ophthalmoscopic examination revealed "ball-shaped tufty hemorrhages along the smaller arterioles." One was at the center of each macula. The hemorrhages cleared up in 1 month. Blood studies were essentially normal, and Baker considered that the hemorrhages were due to increased permeability of the vessels of the retina. Goar[14] reported hemorrhagic extravasations into the retina in 2 patients both of whom were under treatment with sulfathiazole. A woman, aged 34, had received 78 gm. of sulfathiazole in 8 days for the treatment of a pneumonia due to the Type 1 pneumococcus. In the right retina there were 4 globular hemorrhages close to the optic disk; in the upper temporal quadrant of the left retina was a preretinal hemorrhage 3 disk diameters in size. One week later the vision was worse; there was a discrete spherical hemorrhage in each macula. At the end of a month, vision was 20/30 with the right eye and 20/100 with the left. The blood had been absorbed to a great extent. There was no evidence of blood dyscrasia or of renal or vascular disease. In Goar's second case, a woman, aged 37, had received 10.5 gm. of sulfathiazole in 3 days when she complained of blurred vision. Three weeks later, vision was 20/400 with the right eye and 20/25 with the left. Ophthalmoscopic examination revealed in the right macula an area of destruction of the retinal elements and below this a cherry red spot of hemorrhage. The left retina was normal. One week later, vision in the eye was 20/30. Most of the blood had been absorbed from the retina. There was some pigment proliferation in a discrete circular area in the macula.

Three studies have been made which might be said to estimate the visual efficiency of individuals receiving sulfonamides without any gross evidences of toxic reactions. Rosenthal[26] gave 90 to 195 gr. of sulfanilamide to 2 experimental subjects and found that the angioscotomas in the campimetric fields were reduced in width and length. They returned to normal in 4 or 5 days. This change in the scotomas was not due to oxygen deprivation since oxygen deficiency tends to widen the scotomas and since the angioscotomas in the individuals receiving sulfanilamide were not increased in size by giving oxygen. Rosenthal[26] postulated a relative increase in the oxygen present in the region of the retinal synapse or a possible specific influence of the sulfanilamide directly or indirectly on the synapse and on the retinal nutritive state. Alvaro[1] and Silva examined 14 patients for visual acuity, light and color sense, accommodation, muscle balance, state of the media and fundi, ocular tension, and pressure in the central artery of the retina before and after treatment with sulfanilamide, sulfapyridine, and sulfathiazole. No changes were noted in the visual acuity, light and color sense, state of the media and fundi, ocular tension, or pressure in the central artery of the retina. In 1 case, after 30 gm. of sulfathiazole, an exophoria of 4° was reduced to 2°, and in 1 case under sulfapyridine therapy an exophoria of 2° was reduced to 1°. In the other patients muscle balance was not affected. In all but 1 case, however, the power of accommodation was reduced. In 3 cases under sulfacetamide there was an average reduction in accommodative power of 1.33 D. In 4 cases under sulfanilamide with an average blood concentration of 4 mg. per 100 cc., the average reduction in power of accommodation was 1.70 D.

In 2 cases under sulfapyridine with an average blood concentration of 8 mg. per 100 cc., there was a 0.5 D reduction in accommodation in one and no reduction in the other. In 5 cases under sulfathiazole with an average blood concentration of 4.5 mg. per 100 cc., there was an average reduction in power of accommodation of 1.60 D.

Finally, Reynolds, Evans and Walsh[24] studied the effects on visual efficiency of small doses of sulfathiazole or sulfadiazine given for the prophylaxis of gonorrhea and chancroid. Eight subjects were given sulfathiazole and 8 sulfadiazine, 4 gm. in 24 hours at the rate of 1 gm. 4 times a day. Tests were made of the visual acuity, ocular muscle balance, abduction, adduction, fusion and convergence power, accommodation, depth perception, and size of the blind spots for color. The subjects were reëxamined 8 and 32 hours after the last dose. There was no significant change in the visual acuity. There was no alteration in the muscle balance at 20 feet; tests at close range showed a tendency to increased exophoria. Half of the subjects receiving sulfathiazole showed lowered abducting power at the end of 8, but not at the end of 32 hours. Those receiving sulfadiazine showed no change in abducting power. Consistent reduction in the power of adduction was found in the subjects receiving sulfathiazole at the end of 8 hours, but not at the end of 32 hours. Only 1 of the subjects receiving sulfadiazine showed lowered adducting power. There was reduced efficiency of convergence and fusion in half the cases at the end of 8 hours, but this was marked in only 2 of each group. At the end of 32 hours, there was more residual weakness of convergence in the sulfadiazine than in the sulfathiazole group. No consistent effect on the power of accommodation for far or near was noted. One subject who received sulfathiazole showed a definite spasm of accommodation. Depth perception was tested by means of the Howard-Dolman apparatus. The efficiency of depth perception was reduced in half the sulfathiazole and in all the sulfadiazine subjects at the end of 8 hours. In some of the sulfadiazine subjects the deficiency in depth perception was marked and was persistent at the end of 32 hours. The physiologic blind spots were measured on the tangent screen at 33 cm. with $\frac{1}{2}°$ red and blue objects. Two subjects in each group showed a notable increase in the size of the blind spots or a constriction of the color fields. In 5 of the 8 subjects receiving sulfadiazine, the blind spots were found to be slightly abnormal. In the opinion of Reynolds, Evans and Walsh,[24] sulfathiazole and sulfadiazine administered in small "prophylactic" doses are "not without untoward transitory effect on visual efficiency" especially on the ocular muscle balance for near and on depth perception. They are inclined to think that sulfonamides should not be given to men who constantly require maximum visual efficiency, such as pilots, bombardiers, range finders, gun pointers, motorists, locomotive engineers, and precision workers.

REFERENCES

(1.) Alvaro, M. E.: Arch. Ophth., 29, 615, 1943. (2.) Bailey, J.: Am. J. Ophth., 24, 567, 1941. (3.) Baker, J. P., Jr.: Virginia. Med. Month., 67, 562–563, 1940. (4.) Bellows, J. G., and Chinn, H.: Arch. Ophth., 25, 294, 1941. (5.) Bellows, J. G., and Chinn, H.: J. Am. Med. Assn., 112, 2023, 1939. (6.) Blankstein, S. S.: Am. J. Ophth., 24, 895, 1941. (7.) Bloom, W. A., Leech, M. P., and Shaw, W. J.: J. Missouri Med. Assn., 38, 302, 1941. (8.) Bresser, J. S.: Personal communication with M. E. Alvaro. (9.) Bristow, J. H.: Arch. Ophth., 24, 799, 1940. (10.) Bucy, P. C.: J. Am. Med. Assn., 109, 1007, 1937. (11.) Esterman, B.: New York State J. Med., 41, 1646, 1941. (12.) Faenge, G.: Svenska Læk-Tidning, 36, 1197, 1939. (13.) Gailey, W. W.: Am. J. Ophth., 22, 1399, 1939. (14.) Goar, E. L.: Am. J. Ophth., 25, 332, 1942. (15.) Guerra, B.: An. brasil. de oftal., 1, 478, 1942 (quoted by Alvaro, M. E.). (16.) Haviland, J. W.,

and Long, P. H.: Bull. Johns Hopkins Hosp., 66, 313, 1940. (17.) Hornbogen, D. P.: Am. J. Ophth., 24, 323, 1941.

(18.) Liebman, S. D., and Newman, E. H.: Arch. Ophth., 26, 472, 1941. (19.) Mattsson, R.: Acta Ophth., 17, 314, 1939. (20.) Mengel, W. G.: Arch. Ophth., 22, 406, 1939. (21.) Meyer, K., Block, H. S., and Chamberlain, W. P., Jr.: Am. J. Ophth., 24, 60, 1941. (22.) Morrison, W. H.: Am. J. Ophth., 25, 1104, 1942. (23.) Pitter, J.: Casop. Lek. Cesk., 79, 375, 1940. (24.) Reynolds, F. W., Evans, M. S., and Walsh, F. B.: Am. J. Syph., Gon. and Ven. Dis., 27, 2, 1943. (25.) Rittenhouse, E. A.: Arch. Ophth., 24, 1139, 1940. (26.) Rosenthal, C. M.: Arch. Ophth., 22, 73, 1939. (27.) Scheie, H. G., and Souders, B. F.: Arch. Ophth., 25, 1025, 1941. (28.) Scheie, H. G., and Leopold, J. H.: Arch. Ophth., 27, 997, 1942. (29.) Spearman, M. P.: Southwestern Med., 25, 13, 1941. (30.) Spellberg, M. A.: Illinois Med. J., 75, 366, 1939. (31.) Thorne, F. H.: Am. J. Ophth., 22, 430, 1939. (32.) Turkell, J., and Wilhelm, S. F.: Proc. Soc. Exp. Biol. and Med., 47, 97, 1941. (33.) Valdeavellano, J.: Rev. méd. peruana, 11, 556, 1939 (quoted by Alvaro, M. E.). (34.) Volini, I. F., Levitt, R. O., and O'Neil, H. B.: J. Am. Med. Assn., 116, 938, 1941.

It has just come to my attention that R. W. Satterthwaite (J. Urol., 49, 302, 1943) has reported 3 cases of conjunctivitis which occurred among 500 patients under treatment with sulfadiazine, along with other manifestations of toxicity. The conjunctivitis subsided within 3 days after the drug was stopped.

SURGERY

UNDER THE CHARGE OF
I. S. RAVDIN, B.S., M.D.
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BECAUSE of press of war work, there will be no Surgery Progress article in this issue.

BOOK REVIEWS AND NOTICES

BRUCELLOSIS IN MAN AND ANIMALS. By I. FOREST HUDDLESON, D.V.M., M.S., PH.D., Research Professor in Bacteriology, Michigan State College, and the following contributing authors: A. V. HARDY, M.S., M.D., DR.P.H., Associate Professor of Epidemiology, DeLamar Institute of Public Health, Columbia University Medical School Consultant, U. S. Public Health Service; J. E. DEBONO, M.D., M.R.C.P., Professor of Pharmacology and Therapeutics, Royal University of Malta; and WARD GILTNER, D.V.M., M.S., DR.P.H., Dean of Veterinary Division and Professor of Bacteriology, Michigan State College. Third Edition. Pp. 379; 42 figs. New York: The Commonwealth Fund, 1943. Price, $3.50.

WITH this revised edition, appearing 5 years after the first edition, the scope of the book has been broadened to include in addition to methods of laboratory diagnosis, the history, nature, diagnosis, treatment, and control of the disease. Considerable space is devoted to the bacteriology of the disease. "The value of new agents such as vaccines and drug therapy in the treatment of human brucellosis is analyzed, and recent information pertaining to the epidemiology and diagnosis of human brucellosis is set forth." There are appended 26 case reports illustrating different human clinical pictures, with frequent reference to these in the text. In view of some recent reports, it is noted that the relationship of brucellosis to Hodgkin's disease is probably coincidental, for the incidence of Hodgkin's disease in Malta is quite the opposite to the frequency of brucellosis. The authors have assembled in a handy volume practically all the pertinent knowledge related to this subject, and the book should enjoy widespread acceptance and use among bacteriologists, clinicians, veterinarians, and public health workers. M. T.

GYNECOLOGY. By LAWRENCE R. WHARTON, PH.B., M.D., Associate in Gynecology, The Johns Hopkins Medical School; Assistant Attending Gynecologist, The Johns Hopkins Hospital; Consultant in Gynecology, The Union Memorial Hospital, Hospital for Women of Maryland, Sinai Hospital and Church Home and Infirmary. Pp. 1006; 444 illus. Philadelphia and London: W. B. Saunders Company, 1943. Price, $10.00.

DR WHARTON is to be complimented on this production, which includes in one volume, the closely related subjects of gynecology and female urology. The most modern knowledge concerning operative and non-operative phases of gynecology and urology in the female is presented. His organization of the subject is logical and the text is written in very readable form.

The chapter on the anatomy of the pelvic organs is presented with excellent illustrations and a minimum of the usual confusing description. Embryologic development of the local organs is correlated with the occurrence of congenital malformations that are so commonly seen in the urogenital tract. In his discussion of the physiology of the sexual organs the author places particular stress on the recent knowledge concerning the endocrine relationships within the female.

Each organ—the vulva, vagina, cervix, uterus, Fallopian tube, ovary, umbilicus, and appendix—is discussed in detail as to the diseases and their diagnosis and methods of correction. The techniques of the operative treatments are illustrated step by step in large anatomic drawings. A consideration of the complications following gynecologic surgery is not neglected. Methods of prevention and treatment of these conditions are given.

The chapter on the relationships in symptomatology in diseases of the urinary and reproductive organs in women is a particularly helpful presentation for those charged with the responsibility of interpreting the complaints of the female. In this chapter the author emphasizes the bladder, ureteral, and renal symptoms that may be actually caused by gynecologic diseases, as well as abdominal and gynecologic symptoms that are actually due to diseases in the urinary organs. Important considerations in the differential diagnosis of the conditions are presented.

The section on urologic diseases in the female is made up of the following subjects: methods of urologic diagnosis, malformations of the urinary organs, urinary obstruction, non-specific urinary infection, urinary tract tuberculosis, urinary stone, urinary tumor, injury to the urinary tract, and chemotherapy in urinary tract infections. In this section particularly the author presents information that should be of interest not only to the gynecologist, but also the urologist.

Throughout the book each chapter is followed by an extensive bibliography offering excellent reference material for more detailed study of the subject matter.

As a reference book for the gynecologist and urologist, and as a text-book for the student this volume should fill a recognized need.　　　　L. L.

BEHAVIOR AND NEUROSIS: An Experimental Psychoanalytic Approach to Psychobiologic Principles. By JULES H. MASSERMAN, M.D., Assistant Professor of Psychiatry, University of Chicago, and Research Associate, Otho S. A. Sprague Memorial Institute, Chicago. Pp. 269; 7 plates. Chicago: The University of Chicago Press, 1943. Price, $3.00.

ANIMAL experimentation alone has convinced the author of the validity of showing that in a neurosis the fundamental psychodynamic factors are the same as in the more complex emotional disturbances of human beings. While a few dogs were used, most of the subjects were cats, as accidental stimuli affect them less, and their inhibitory functions being weaker, behavior shows less domination. Part I considers historical data and the results of laboratory experiments; Part II surveys pertinent literature on dynamic and experimental neuroses; Part III attempts the clinical application of such data. "To establish symbol-reactive and goal-directive patterns of behavior adaptation, animals were trained in an automatic apparatus to lift the lid of a box to secure food in response to one or more stimuli in various sensory modalities." Frustration and conflict, the result of mechanically induced fear and anxiety, are said to have so affected animal behavior that the subjects became "neurotic" or "psychotic." The bibliography exceeds more than 1000 titles.
　　　　　　　　　　　　　　　　　　　　　　　　　　　N. Y.

THE INFECTIOUS DISEASES OF DOMESTIC ANIMALS. By WILLIAM ARTHUR HAGEN, D.V.M., D.Sc., Professor of Bacteriology and Dean of the Faculty, New York State Veterinary College, Cornell University. Pp. 665; 145 illus. Ithaca, N. Y.: Comstock Publishing Company, 1943. Price, $6.00.

THIS is a well-integrated and entirely adequate account of the host of infectious diseases to which domesticated mammals and birds are subject, of the specific microorganisms involved and of available methods of diagnosis and control. The introductory section of the book is a consideration of the general aspects of infection and disease production by microorganisms, and of the nature and development of the immune response, with a brief review of allergic conditions and of its antibodies. Discussion of groups of microorganisms is arranged under the following section headings: Pathogenic Bacteria, Bacteria like Pathogenic Organisms of Uncertain Classification, i. e., Spirochetes, Rickettsia and Pleuro-pneumonia, Pathogenic Fungi, Pathogenic Protozoa.

and Viruses. For each of these groups or, where justified, for individual organisms, consideration follows the general pattern: morphology, reactions in culture, natural habitat, pathogenicity and types of disease in susceptible hosts, diagnostic and control methods, immune response, and, where appropriate, relation to disease of man. Each chapter and many chapter subdivisions have short lists of well-chosen references appended. This is not a textbook of bacteriology in the usual sense, but combines the several aspects of infectious disease to form one that seems a well-worthwhile addition to the texts which have been available in this field.   H. R.

BEHIND THE SULFA DRUGS—A SHORT HISTORY OF CHEMOTHERAPY. By IAGO GALDSTON, M.D., with a Preface by PERRIN H. LONG, M.D., Associate Professor of Medicine, Johns Hopkins University. Pp. 174. New York: D. Appleton-Century Company, Inc., 1943. Price, $2.00.

THE author has described in non-technical language the development of chemical weapons against infectious diseases from ancient times to the present day. An appropriately generous portion of the book is devoted to the story of Paul Ehrlich and of his influence for and against progress in this field. Of particular interest is the discussion of "The Doldrum Years" from the time of Ehrlich until 1935 when the discovery of sulfonamide therapy was announced. These were the years when sulfanilamide remained on the chemists' shelves and escaped recognition as a chemotherapeutic agent, while most investigators continued to be ineffectively preoccupied with the possibilities of synthetic dyes in treating infections. This is a very interesting book and will be enjoyed equally by those with specialized or general interest in medical science.   J. L.

TRANSURETHRAL PROSTATECTOMY. By REED M. NESBIT, M.D., F.A.C.S., Associate Professor of Surgery, University of Michigan Medical School, in charge of the Section of Urology, Dept. of Surgery. With original drawings illustrating techniques by WILLIAM P. DIDUSCH. A Chapter on the Vascular Supply of the Prostate Gland by RUBIN H. FLOCKS, M.D. Pp. 201; 62 plates. Springfield, Ill.: Charles C Thomas, 1943. Price, $7.50.

DR. NESBIT is recognized as one of the experts in the field of prostatic resection. His book records, in an excellent manner, his technique of surgery and methods of patient care.

The first chapter on arterial distribution within the prostate is based on the original work of Dr. Rubin H. Flocks. A knowledge of the circulation of the prostate is basic in the technique of prostatic resection. There is a chapter on the history of the development of the resectoscope.

This book should be of great value to anyone doing prostatic surgery as well as to anyone concerned with the care of prostatic patients.   L. L.

SOCIAL INFLUENCES AFFECTING THE BEHAVIOR OF YOUNG CHILDREN. By RUTH PEARSON KOSHUK. Monographs of the Society for Research in Child Development, Vol. VI, No. 2 (serial No. 28). Pp. 71. Published by the Society for Research in Child Development, National Research Council, Washington, D. C., 1941. Price, $1.00.

THIS is a carefully organized survey of the significant research publications since 1925, dealing with the behavior of young children as influenced by social factors. The divergent points of view in this branch of "social psychiatry" are presented thoughtfully and with fairness. An extensive bibliography is appended.
                    I. W.

THE THERAPY OF THE NEUROSES AND PSYCHOSES. By SAMUEL HENRY KRAINES, M.D., Associate in Psychiatry, University of Illinois, College of Medicine; Assistant State Alienist, State of Illinois; Diplomate of American Board of Psychiatry and Neurology; Captain, United States Medical Corps. Pp. 567; 6 figs. Second ed. Philadelphia: Lea & Febiger, 1943. Price, $5.50.

CAPTAIN KRAINES is at present a military lecturer on Psychiatric Orientation, at Fort Hood, Texas. This book of 20 chapters, written in excellent English, designed for the student and general practitioner, is a thoroughly revised second edition within 2 years. The space previously allotted to Psychoanalysis and Related Schools is reduced. Schizophrenia is discussed more fully, and there are additional chapters on Shock Therapy, the Organic Psychoses, Psychiatric Interview Techniques, and the Neuropsychiatric States Induced by War.

During the present wartime period, neuroses occur among the civil population because of; "(1) fear of personal attack or injury, (2) threat of economic insufficiency, (3) dangers of inadequate food supply . . . ., (4) threat of separation of family, and (5) disturbance of a routine manner of living. . . . ." Under Neuropsychiatric States in Military Service, the following are some of the topics discussed: such states among drafted men before army admission, and among military forces not in actual combat; such states under combat conditions; prophylactic therapy; tension symptoms; symbolic symptoms; therapy of acute neuropsychiatric states; shell shock; front line therapy; group psychotherapy; therapy in neuropsychiatric centers; individual therapy; desensitization; group hypnosis; socialization; and the return to active combat of those soldiers already cured.

Many of the socio-psycho-biologic problems of present-day civil and military life are ably discussed here. Over 200 illustrative cases are used, and there is an exceptionally comprehensive index of more than 35 pages. The writer's purpose of providing a practical understanding of neuropsychiatric states, with concrete suggestions on treatment, is sustained throughout.

N. Y.

AS THE TWIG IS BENT. By LESLIE B. HOHMAN, M.D., Associate in Psychiatry, Johns Hopkins Medical School; Assistant Visiting Psychiatrist to the Johns Hopkins Hospital. Pp. 291. New York: The Macmillan Company, 1943. Price, $2.50.

THE most striking point in this delightful book is its plain, common sense approach to the problem of raising children to be well-adjusted adults. Seven reprintings of this first edition testify to its popularity. Dr. Hohman is, without doubt, well versed in his field, as is evidenced by the wide variety of experiences he has had in dealing with children.

The style of his writing is simple, clear and essentially conversational. Case studies are not set down in the clinical style so often associated with a technical book; but they are used to illustrate a point the author is making at that particular minute set forth in a few paragraphs and applied directly to the point in question. Problems that are discussed in the book are those that arise with a child's progressing age; and yet in many instances these problems have their roots in or near the child's infancy.

The book gives the reader a feeling of confidence that he, the reader, could be almost an exemplary parent if he made up his mind to spend the same amount of time, thought, interest in and preparation on becoming and being a parent as he does for a career, that he could be as successful in one as in the other with the same amount of satisfaction in a job well done. Changed conditions in modern societal life have brought to the attention of the lay public the problems arising in marriage. So, too, we are recognizing the problems of modern parenthood and are striving to do something about them.

The Reviewer recommends this book highly to all those who care about to

become parents and to those who already are parents. One reading is not enough, for this is the type of book one will want to refer to many times to reassure himself that the course he is trying to steer is the best for all concerned.

E. F.

CIVILIAN HEALTH IN WARTIME. By FRANCIS R. DIEUAIDE, M.D., Associate Professor of Medicine, Harvard Medical School, Massachusetts General Hospital. Pp. 328; several tables. Cambridge, Mass.: Harvard University Press, 1942. Price, $2.50.

"This book represents an attempt to provide the general reader with a statement, in broad but definite outline, of the varied aspects of health in the United States in relation to the war. The point of view is that of positive health. Hence diseases are not described; nor are methods of treatment presented. . . . The aim of our enemies is to destroy our health, but through our health we shall defeat them."

This quotation is from the preface and indicates the author's serious purpose. The book is in readable though scholarly style, contains an abundance of well-chosen illustrations to emphasize the many points that are made, and discusses community and mental health problems as well as those of individual health. Nutrition, diet, geriatrics, occupation, recreation, medical and nursing services, mental calm and vigor and morale are given detailed discussion. The non-professional student of social science and current world problems who seeks an understanding of America's medical resources and attitudes in these critical years will find here a well organized, panoramic presentation free from subjective bias.

I. W.

DIE APPETITLOSIGKEIT IM KINDESALTER. By JULIUS SURANYI, Obenarzt am Stefanie Kinderspital (1940). Verlag von S. Karger in Basel (Switzerland). Pp. 128. For U. S. A.: New York: Nordeman Publishing Company, Dept. S. Karger, 215 Fourth Avenue. Price, S.fr. 6.

THIS monograph is a well-conceived and thoughtful survey of the problem of anorexia in infancy and childhood. The author's classification of the types of anorexia and of the types of children with the complaint is well done. Fully aware that loss of appetite is at best a symptom, the author outlines systematically the methods for studying the infant and child with anorexia. This study outline is an excellent, brief review of pediatric gastro-enterologic diagnostic procedure.

There is a detailed analysis of the somatic and psychologic factors responsible for acute or chronic loss of appetite. The discussion of the somatic factors is thorough and is cognizant of recent developments, e. g., the rôle of infestation with *Giardia lamblia* as a disturbing influence. The section dealing with the psychologic aspects of anorexia is equally thorough, but the inclusion of a great deal of abstract speculative discussion does not make for clarity.

The therapeutic recommendations are sound and in accord with current pediatric and psychiatric procedure.

This monograph should be of interest to pediatricians and to psychiatrists concerned with child guidance.

M. R.

ADVANCES IN PEDIATRICS. Edited by ADOLPH G. DESANCTIS, M.D., New York Post-Graduate Medical School and Hospital, Columbia University, N. Y., and several associate editors. Pp. 306; many figs., plates and tables. New York: Interscience Publishers, Inc., 1942. Price, $4.50.

EACH chapter in this auspicious first volume of a projected annual series deals with some pediatric subject which has seen constructive progress within

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the past few years. The contents comprise 9 short "personalized monographs," on Toxoplasmosis (Sabin); Virus Diseases (Hodes); Chemotherapy (Carey); Electroencephalography (Brill); Vitamin K in the Newborn Period (Poncher); Surgery of Persistent Ductus Arteriosus (Gross); The Premature Infant (Tow); Tuberculosis (Nelson); Endocrinology (Gordon), together with 9 "abstracts of some other advances in pediatrics" (DeSanctis and Pittinos). The authors of the major chapters are well known for special studies within their respective fields.

The quality of every article is excellent, and the style lucid and easy to read. This book is of importance not alone to specialists in pediatrics, who will find therein well-organized formulations of authoritative current points of view. It can be highly recommended as useful both to alert general practitioners who want to keep abreast of advances in this branch of medicine, and to internists and other specialists who desire an understanding of the early stages of some of the long-standing disorders of adult patients which often date back to childhood years.

I. W.

MANUAL OF INDUSTRIAL HYGIENE AND MEDICAL SERVICE IN WAR INDUSTRIES. Edited by WILLIAM M. GAFAFER, D.Sc. Issued under the Auspices of the Committee on Industrial Medicine of the Division of Medical Sciences of the National Research Council. Prepared by the Division of Industrial Hygiene, National Institute of Health, U. S. Public Health Service. A composite book with 16 contributors. Pp. 508; 20 illus. Price, $3.00. London: W. B. Saunders Company, 1943. Philadelphia and

THIS excellent manual, as its name implies, is dedicated to industrial hygiene and medical services in war industries. The contributors, whose painstaking work has made this book possible, have been chosen because of their outstanding ability in the subject which they present.

The volume is presented in 3 parts: Part 1: Organization and Operation of Facilities, contains the following chapters: War's Influence on Industrial Hygiene; Plant Medical Facilities; Organization of Plant Medical Department: Medical, Nursing, and Dental Services; Organization of Plant Emergency Services; and Available Services in Industry, is in 2 sections: Section 1 covers the problem of Occupational Dermatoses; Medical Control of Respiratory Diseases; Venereal Disease Control, Industrial Psychiatry, Health Education, Fatigue and Nutrition. Section 2 covers Community and Plant Sanitation, Illumination, Noise, and Radiant Energy, Heating, Ventilation and Air Conditioning. Part 3: The Manpower Problem, discusses the subject of maximum use of manpower, Women in Industry and Absenteeism. Appropriate bibliographic references accompany each chapter.

This book is most timely and is seriously recommended to all physicians, hygienists, safety men, and nurses engaged in industrial work.

R. K.

observations. Audiometric curves in childhood were found to assume the same characteristics as in adults. There was a strong tendency for the two ears of the same child to give the same type of audiometric curve. The incidence of high tone loss increased with advancing age and was greater in boys than in girls. Hearing impairment was often associated with past or present inflammatory lesions of the tympanic membranes, but bore no relationship to the condition of nose and tonsils as observed at the time of the examination. From these data the authors conclude that about 5% of America's school children (close to 1½ millions) possess impairment of hearing in one or both ears sufficiently marked to become a handicap. Another fraction of equal size is estimated to suffer from high tone loss, a defect which does not interfere with daily life, though in certain situations it may be noticeable and annoying. By proper testing incipient deafness can be detected in its early subclinical stages. "It is only too obvious, therefore, that even a small loss of acuity cannot be disregarded if successful results are to be hoped for in preventing deafness; especially since very few ears with impaired hearing appear to improve when the impairment has reached the level here defined as marked." I. W.

A STUDY OF ENDOMETRIOSIS, ENDOSALPINGIOSIS, ENDOCERVICOSIS AND PERITONEO–OVARIAN SCLEROSIS. A CLINICAL AND PATHOLOGICAL STUDY. By JAMES R. GOODALL, M.D., D.Sc., Formerly Professor of Gynecology and Obstetrics, McGill University. Pp. 140; 19 figs. Philadelphia: J. B. Lippincott Company, 1943. Price, $5.50.

GOODALL has brought together under one cover all essential knowledge dealing with the whole subject of endometriosis, the first time that this has been done. It includes several chapters dealing with previously unpublished work in the field. The history of the subject is reviewed. The volume has a decidedly clinical slant; it deals with the question of diagnosis, records the latest developments in research, indicates how the condition spreads and speculates upon its causation. There are 13 illustrations in black and white and 17 subjects in full color. The observations appear to be largely those of the author, and the list of references relatively short. The book is one which should be in the library of every gynecologist, and might well be consulted by medical students during their clinical years when studying gynecology. D. M.

THE CHEMISTRY OF NATURAL COLORING MATTERS. THE CONSTITUTIONS, PROPERTIES, AND BIOLOGICAL RELATIONS OF THE IMPORTANT NATURAL PIGMENTS. By FRITZ MAYER, PH.D., Formerly Professor of Chemistry in the University of Frankfort-on-Main. Translated and revised (from the third and last German edition) by A. H. COOK, PH.D., Department of Chemistry, Imperial College of Science, London). American Chemical Society Monograph No. 89. Pp. 354. New York: Reinhold Publishing Corporation, 1943. Price, $10.00.

THIS volume is an addition to the growing number of authoritative scientific monographs published under the sponsorship of the American Chemical Society. It is an excellent critical discussion, almost exclusively of an organic chemical nature, upon several hundred pigments of plant and animal origin. The book is divided into 5 chapters, each of which embraces pigment derivatives belonging, from the standpoint of structure, to a different chemical class.

The chapters upon "Polyene Pigments" and "Heterocyclic Nitrogen Atoms" embrace commonly met substances, such as the carotenoids (including vitamin A), porphyrin derivatives of hemoglobin and chlorophyll, pterins, and flavins. The larger part of the text, however, is devoted to less well-known pigments, discussed mainly under the heads of "Carbocyclic Compounds" and "Heterocyclic Compounds."

The book is published posthumously. Professor Cook, the translator-editor, records in a preface that Professor Fritz Mayer "died in July, 1940, in circumstances which, it need only be said, were as sad as any imaginable." The Reviewer recommends the book as a useful reference work in its field, covered comprehensively and withal briefly.   D. D.

MILITARY SURGICAL MANUALS. V. BURNS, SHOCK, WOUND HEALING AND VASCULAR INJURIES. Prepared under the Auspices of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 272; 81 figs. Philadelphia and London: W. B. Saunders Company, 1943. Price, $2.50.

MANY distinguished American surgeons have collaborated to produce this book. Each of the subjects named in the title has been subdivided into many chapters, and each chapter summarizes the views and experiences of one or several men on the topic in question. It is presumed that all statements have been reviewed editorially by the respective subcommittees of the Committee on Surgery. The book was designed to familiarize doctors being called into military service with current concepts in certain provinces of military surgery, and one can say that this purpose is well fulfilled. An abundance of useful non-controversial information is contained herein. Some matters receive more emphasis than others of equal or greater importance, for example, more space is allotted to the arteritis:scalenus syndrome than to the treatment of varicose veins by injection, but such lack of evenness can be excused by the multiplicity of authorship. The illustrations are excellent.   I. W.

MEDICAL JURISPRUDENCE AND TOXICOLOGY. By JOHN GLAISTER, M.D., D.Sc., Fellow of the Royal Faculty of Physicians and Surgeons, Glasgow; of the Inner Temple, Barrister-at-Law, etc., Regius Professor of Forensic Medicine, University of Glasgow; Formerly Professor of Forensic Medicine, University of Egypt, Cairo; and Medico-Legal Consultant to the Egyptian Government. Pp. 671; 132 illus. Seventh ed. Baltimore: The Williams & Wilkins Company, 1942. Price, $8.00.

IN its 7th edition, the form of this standard text has been recast and it has been for the most part rewritten; many illustrative cases are new. In the section on Toxicology some new poisons have been added, notably the sulfa drugs (sulfanilamide, sulfapyridine and sulfathiazole); and the tests for the identification of poisons have been limited, except in a very few instances, to qualitative tests, in recognition of the specialized character of quantitative toxicologic procedures. A chapter on war gases and the effects of blast has been added, and a special appendix on procedures in deaths following air raids.

The book is very well illustrated and indexed. The laws cited are limited to those of England and Scotland, and in this one respect the book does not meet completely the needs of the American reader.   E. W.

The original plan of a biologically oriented neurology has been maintained without sacrificing practical diagnosis and therapy. The 22 chapters of the book cover practically the entire field of Neurology. Many illustrations of electroencephalography and pneumoencephalography greatly clarify the text. Advances in the study of encephalitis and the function of the hypothalmus are well covered. The subject of aphasia is too briefly described but adequate references are given. Separate chapters on the epilepsies and headache include the most recent ideas as to etiology and treatment. Trauma of the central nervous system is thoroughly considered, including herniation of the nucleus pulposus; but the medico-legal aspect of the subject is unfortunately omitted. The book is well indexed and contains many new illustrations and valuable tables. Recent literature has been added without deletion of the most important older literature. A change of typography adds to the ease of reading. This excellent textbook of Neurology is highly recommended.   A. S.

CLINICAL SIGNIFICANCE OF THE BLOOD IN TUBERCULOSIS. By GULLI LINDH MULLER, M.D., Pathologist and Director of Laboratory, New England Hospital for Women and Children, Boston; Formerly Pathologist, Rutland State Sanatorium, Rutland, Mass. Pp. 516; 52 tables, 19 charts. New York: The Commonwealth Fund, 1943. Price, $3.50.

THE importance of the blood picture in tuberculosis is not generally appreciated. Dr. Muller's book is a complete critical review and correlation of the literature on the subject, combined with an analysis of 6819 blood examinations done on 1000 patients over 5 years. The text is well organized (including a complete Bibliography) and the contents are divided into 6 parts: the first being a summary of the physiology of the hemopoietic system and its response to the tubercle bacilli; Part 2 discusses the changes and response of the various cellular elements both qualitatively and quantitatively in tuberculosis. Part 3 dealing with the sedimentation rate is a complete review of the subject, stressing the importance of this test in tuberculosis and presenting a new table for corrections. Parts 4 and 5 compare clinical and hematologic data in various stages and types of diseases, methods of treatment and complications, demonstrating that the blood picture and sedimentation rate give information, not otherwise obtainable, concerning the status of the disease and its prognosis. Part 6 gives in detail her methods. This book fills a very definite need in the field of tuberculosis and should be read by every phthisiologist.   D. C.

ESSENTIALS OF INDUSTRIAL HEALTH. By C. O. SAPPINGTON, M.D., DR.P.H., Consulting Industrial Hygienist, President, Central States Society of Industrial Medicine and Surgery; Editor of "Industrial Medicine." Pp. 626; 63 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $6.50.

THIS text is the most recent addition to a long list of outstanding contributions, by one of the foremost medical authorities in the industrial field. It is a comprehensive undertaking and presents a panorama of all the phases of industrial health, designed particularly to aid those already in this type work, and especially to familarize those, either new in the field or contemplating such a change.

The book makes for quick and easy reading, and is presented in 3 parts. The first, Industrial Health Administration, ranges from an excellent chapter on the history of industrial medicine, through legislative background to rehabilitation of workers. The second third discusses Industrial Hygiene and Toxicology with chapters on Exposures, Plant Survey, Plant Sanitation and Hygiene, Personal Hygiene. The final third is on Industrial Medicine and Traumatic Surgery, covering the Worker, Accidents, Occupational and Nonoccupational Conditions, plus Workmen's Compensation and Rehabilitation.

In the Appendix there is technical material of great value, plus a well-selected Bibliography.

This book is heartily recommended as a ready reference book for all interested in this most important field.   R. K.

A GUIDE TO PRACTICAL NUTRITION: A series of articles on nutrition, sponsored by the Committee on Nutrition and Deficiency Diseases of The Philadelphia County Medical Society. Edited for the Committee by MICHAEL G. WOHL, M.D., and JOHN W. WILLARD, M.D. Pp. 98. The Philadelphia County Medical Society, 1943.

As stated in the introduction by Dr. Morris Fishbein, this committee "rendered a distinct service by publishing in *Philadelphia Medicine* some of the basic facts in the field concerned. This material was so favorably received that it is now being extended with the aid of John Wyeth and Bro., Inc., to a much larger audience." It consists of concise but adequate chapters on most of the clinical aspects of nutrition with many suggested diets. In the appendix is a vitamin chart and a table of food composition, weights, and measures.

                                                                M. T.

WAYS OF THE WEATHER. By W. J. HUMPHREYS, A.B., C.E., PH.D., Sc.D., Meteorological Physicist (Retired, Collaborator), U. S. Weather Bureau. Pp. 400; 75 illus. Lancaster, Pa.: Jaques Cattell Press, 1942. Price, $4.00.

THIS volume is one of a "humanizing science series" written for the lay public. It is written in a rather simple manner and succeeds in giving the reader a good, basic understanding of the weather and the factors involved in producing it. In 16 chapters the author presents in satisfactory detail a rather complete treatise from the origin and composition of the atmosphere and the rôle played by each of its constituents in the production of wind, precipitation, temperature, pressure, and so forth, to the application and influence of weather both bad or good on our lives. This book not only is enjoyable to read, but also substantially enhances our knowledge of the most talked about peacetime subject, the weather.   M. T.

The Role of Nutritional Deficiency in Nervous and Mental Disease. Vol. XXII. Proceedings of the Association Dec. 19 and 20, 1941, New York. Editorial Board: STANLEY COBB, M.D., Chairman, EDWIN F. GILDEA, M.D., HARRY M. ZIMMERMAN, M.D. Pp. 215; 23 illus., 8 tables. Baltimore: Williams & Wilkins Company, 1943. Price, $4.00.

Human Neuroanatomy. By OLIVER S. STRONG, Formerly Professor of Neurology and Neurohistology, College of Physicians and Surgeons, Columbia University; and ADOLPH ELWYN, Associate Professor of Neuroanatomy, College of Physicians and Surgeons, Columbia University. Pp. 417; 320 figs. Baltimore: Williams & Wilkins Company, 1943. Price, $6.00.

Air-borne Infection. By DWIGHT O'HARA, M.D., Professor of Preventive Medicine, Tufts College Medical School; Visiting Physician, Boston City Hospital; Physician-in-Chief, Waltham Hospital. Pp. 114; several charts and tables. New York: The Commonwealth Fund, 1943. Price, $1.50.

Textbook of Anatomy and Physiology for Nurses. By CARL C. FRANCIS, A.B., M.D., Senior Instructor in Anatomy, Department of Anatomy, Western Reserve University, Cleveland; G. CLINTON KNOWLTON, PH.D., Assistant Professor of Physiology, College of Medicine, State University of Iowa; and W. W. TUTTLE, PH.D., Professor of Physiology, College of Medicine, State University of Iowa. Pp. 586; 338 illus. (38 color plates). St. Louis: C. V. Mosby Company, 1943. Price, $3.50.

Skin Grafting of Burns. By JAMES B. BROWN, M.D., LT.-COL., M.C., U. S. A., Senior Consultant in Plastic and Maxillo-facial Injuries and Burns, E. T. O., U. S. A., Associate Professor of Surgery, Washington University, St. Louis; and FRANK McDOWELL, M.D., Assistant in Clinical Surgery, Washington University. Pp. 204; 131 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $5.00.

Your Arthritis: What You Can Do About It. By ALFRED E. PHELPS, M.D., Introduction by R. GARFIELD SNYDER, M.D. Illustrations by JAMES MacDONALD. Pp. 192; 12 illus. New York: William Morrow & Co., 1943. Price, $2.00.

Essentials of Syphilology. By RUDOLPH H. KAMPMEIER, A.B., M.D., Associate Professor of Medicine, Vanderbilt University School of Medicine; in Charge of the Syphilis Clinic and Visiting Physician to Vanderbilt University Hospital. With chapters by ALVIN E. KELLER, M.D., and J. CYRIL PETERSON, M.D. Pp. 518; 87 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $5.00.

The Common Form of Niacin Amide Deficiency Disease: Aniacinamidosis. By WILLIAM KAUFMAN, PH.D., M.D. Pp. 62. Bridgeport, Conn.: Yale University Press, 1943. Price, $3.00.

NEW EDITIONS

The Practice of Refraction. By SIR STEWART DUKE-ELDER, M.A., D.Sc. (ST. AND.), PH.D. (LOND.), M.D., CH.B., F.R.C.S., Surgeon-Oculist to H. M. The King; Ophthalmic Surgeon and Lecturer in Ophthalmology, St. George's Hospital. Fourth ed. Pp. 328; 183 illus. Philadelphia: The Blakiston Company, 1943. Price, $4.50.

Injuries of the Skull, Brain and Spinal Cord. Edited by SAMUEL BROCK, M.D., New York University. Second ed. Pp. 616; 78 figs. Baltimore: Williams & Wilkins Company, 1943. Price, $7.00.

The Therapy of the Neuroses and Psychoses. By SAMUEL H. KRAINES, M.D., Associate in Psychiatry, University of Illinois, College of Medicine; Assistant State Alienist, State of Illinois; Diplomate of American Board of Psychiatry and Neurology; Captain, M.C., U.S.A. Second ed. Pp. 567; 5 figs. Philadelphia: Lea & Febiger, 1943. Price, $5.50.

ORIGINAL ARTICLES

FURTHER HISTORICAL AND EXPERIMENTAL STUDIES ON MENSTRUAL TOXIN*

By David I. Macht, M.D., F.A.C.P.

BALTIMORE, MD.
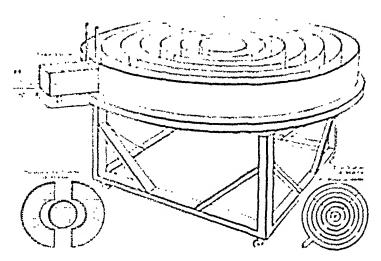
(From the Pharmacological Research Laboratory, Hynson, Westcott & Dunning, Inc.)

Introduction. Nearly 20 years ago the present writer and Miss Lubin published their studies on menstrual toxin, which for the first time set forth scientifically controlled experimental data demonstrating the presence of a toxic substance—menotoxin—in the blood and other tissues of menstruating women.[82a,b] It is true that popular belief and folklore of all races throughout all time have ascribed a contaminating influence to women's touch during the menses but no experimental proof of such a poison has been handed down in the literature, and indeed with the rise of modern medicine the empirical taboos of older physicians and laymen have been derided as fantastic by scientists who never troubled themselves to make a disinterested scientific inquiry into the subject. We are therefore greatly indebted to Bela Schick for reviving the interest of the medical world in one of these superstitions, namely, the wilting of flowers handled by menstruating women, and for carrying out some tests on flowers they touched, the results of which suggested that there was even more contamination in such contact than superstition indicated. Professor Schick[120] admitted, however, that his experiments were not absolutely conclusive from the strictly scientific point of view. By a happy coincidence Macht and Livingston were working about that time in the laboratory for plant physiology at the Johns Hopkins University and engaged in the comparative study of the effects of various drugs and chemicals on living animal and plant tissues.[81] The results of these comparative experiments indicated at an early date that living plant physiologic test objects may be more sensitive to the deleterious effects of certain poisons than living animal tissues treated with the same poisons. Such an observation suggested an approach by phytopharmacologic methods to the search for small quantities of toxic substances in the blood and other secretions of animals and thus was discovered a new branch of biology to which the name of *phyto*pharmacology was

rine not unlike that effected in smooth muscle preparations for the same drug by applications of thyroxin.[4] Menstrual serum was also found to be toxic for paramecia and goldfish and the authors also described experiments on the sciatic nerves of rats which indicated that applications of menstrual serum killed the activity of these nerves sooner than did normal human blood serum in control experiments. Findings reported also by Macht and Hyndman[79a] revealed that injections of menstrual serum were very depressant for the behavior of rats trained to run in the circular maze. The paper of Macht and Davis, read before the Section on Psychology of the American Association for the Advancement of Science in 1932, and embodying new material and reviewing data published on this subject by foreign investigators, appears to have given some impetus to the study of menstrual toxin for a number of interesting and important experimental and clinical studies have appeared in European literature since that date. In the following paper the writer wishes to present the new experimental data concerning menotoxin gathered in the laboratory and to review the literature appearing on the subject in the past 10 years with a view to correlating the considerable store of scientific data concerning menstrual toxin which has been published with the older empirical information gleaned from folkloristic accounts on the subject and of discussing these data with regard to their significance in clinical medicine.

Experimental Psychologic Studies. Inasmuch as the most striking clinical symptoms in women at catamenia have to do with the nervous system, the writer, who has always been interested in psychopharmacologic effects of drugs—that is, their action on neurologic functions—undertook an extensive experimental investigation of the psychologic effects of menotoxin on albino rats. Specimens of menstrual serum were obtained from various individuals and after their toxicity had been established by phytopharmacologic tests on *Lupinus albus* seedlings, they were placed in the icebox, various doses being injected into rats and employed in psychologic tests. Three lines of investigation were followed in this research. In the first series of experiments the effect of normal serum and of menstrual serum injected into rats was studied on their behavior in the circular maze. The apparatus employed was a modification of the original Watson apparatus and is reproduced in Figure 1. Food was placed in the center of the maze and the rats were trained to thread the runways to the food in the shortest time possible without running into blind alleys. Once the animals have learned the maze their performance is remarkable for they run with clocklike precision by the shortest route, often in but 5 seconds from the periphery to the center of the apparatus, without a single mistake. Such trained rats are admirably adapted to the study of the effects of drugs or poisons on the neuromuscular behavior and what may be termed the higher psychologic functions of the animals and have often been employed by the author for that purpose.[73,85,87] Whatever theories are advanced concerning rats learning the maze problem, all authors agree that such a performance involves not only a response to propriosensitive stimuli but also a choice reaction or

discrimination.[33] The goal gradient, the food placed in the center of the maze, is one basis for the blind alley elimination, and the animal uses its sense of discrimination and judges the shortest path to the goal under the hunger drive. But the maze problem involves other factors which Woodworth describes in detail.[40] The rat learns its

Fig. 1. Circular maze.
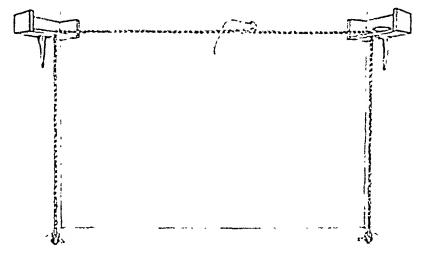
Fig. 2. Test for neuromuscular coördination.

way from the periphery to the center of the maze by distinguishing objects in their spatial relations and in learning these in terms of a total pattern must exercise some function of higher nerve centers than those concerned with simple reflex responses.

A second series of psychologic experiments was made on rats trained to walk the tight rope, like the acrobat, from one platform to another

where food had been placed. This exercise involved a delicate neuro-muscular coördination of the animals and after much training the rats learned to balance themselves very well and ran from one end of the rope to the other in very short time. Such a setup, illustrated by Figure 2, has been employed by Macht and Ulrich[88] for psychopharmacologic work.

A third series of experiments was made with rats trained to climb another 5-foot rope fastened to the floor at one end and to a platform holding food, on the other, an exercise involving neuromuscular co-ordination but especially designed for testing the ergographic or work
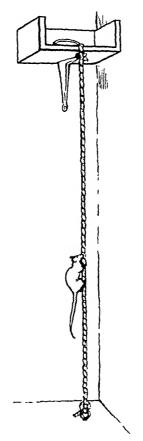
Fig. 3.—Test involving neuromuscular coördination and work capacity.

capacity of the skeletal muscles. The writer does not know of any previous published work in which such a test was employed. This setup is shown in Figure 3.

Experiments were made on 24 adult rats, 12 male and 12 female, injected on various days with normal human sera and with menotoxic sera. To avoid anaphylactic reactions, which are not very common in rats, the writer was careful not to repeat the serum injections after long intervals.

Table 1 shows the results obtained in 21 experiments. It will be seen that some animals were taught all 3 forms of exercise while others were used in but 1 or 2 of the tests. The effect of menotoxin

varied with the dosage and also with the toxicity of the sera determined by phytopharmacologic methods. There was no doubt about the poisonous nature of menstrual serum for a sufficiently large dose will kill a rat. Two such casualties, of a male and a female rat, respectively, are noted in the table, which does not show the results of other tests that the writer made in this connection. Small doses of menotoxic serum, as compared with the controls, profoundly depressed the neuromuscular system. It will be noted that such injections were particularly disturbing in the rope-walking and rope-climbing experiments, thus indicating the depressant action of this toxin on the muscles. In most cases also the activity of the rats in the maze was definitely impaired as the slower movements and longer running time of the animals as well as the occasional errors they made plainly indicated. These findings agree with those obtained by Macht, Hyndman and Davis. The toxicity of large doses of menotoxin for rats has recently been described also by Smith and Smith.[12]

TABLE I   RESULTS OF MENOTOXIN EXPERIMENTS ON ALBINO RATS

Exp. No.	Sex of rat	Nature of Substance injected		Rope Distance Before After		Walk Distance Before After		Climb Distance Before After	
1	F	Control: Ringer 0.9%	1.0 cc	6.3	6.0	6.3	5.0	8.0	13
2	F	Control: P.N. serum	0.5 "	6.0	7.0	4.6	5.0	9.0	13
3	F	Menotoxin serum (L)	0.25 "	6.0	25.0	5.3	6.0*	11.0	Stalled
4	F	Menotoxin serum (L)	0.35 "	5.6		6.6		10.3	Died
5	F	Control: normal serum	0.3 "	5.6 6.0	5.6				
6	F	Control: normal serum	0.3 "	11.0	8.6 7.3				
7	F	Control: pemphigus serum	0.5 "	6.0	5.0				
8	F	Menotoxin serum (S)	0.1 "	6.0	6.3				
9	F	Menotoxin serum (S)	0.2 "	6.3	8.0				
10	F	Menotoxin serum (S)	0.3 "	6.0	8.0				
11	M	Control: normal serum	0.1 "	5.6	5.0	5.6	5.6		
12	M	Control: normal serum	0.75 "	6.6	6.6				
13	M	Menotoxin serum (S)	0.2 "	5.0	6.0				
14	M	Menotoxin serum (S)	0.3 "	5.3	6.6	6.0	5.6		
15	M	Menotoxin serum (X)	0.4 "	6.3	Stalled			6.6	Stalled
16	M	Menotoxin serum (X)	0.3 "	6.6	7.3				
17	M	Menotoxin serum (B)	0.5 "	8.0	19.0		Stalled	8.1	Stalled Died
18	M	Control: normal serum	0.5 "	6.0	5.0				
19	M	Menotoxin serum (S)	0.5 "	6.0	8.0				
20	M	Menotoxin serum (S)	0.2 "	5.0	6.0	5.6	5.0		
21	M	Menotoxin serum (S)	0.3 "	6.0	8.0	6.3	7.0		
					25.0* 19.0*				

* Superimposed figures indicate number of errors.

Absorption of Poisons Through the Male Genitalia. In order to determine whether or not menstrual poison can exert a deleterious effect on the human male or, more specifically, on the mates of menstruating women, the writer began a series of experiments dealing with the broader question of possible absorption of drugs and poisons through the male genitalia. The method of approach was like that which he used for many years in studying absorption of drugs through other unusual channels such as the eye,[71c] ear,[71f] urethra,[71d] esophagus,[71g] vagina,[71e] and skin.[71a,f] Experiments were made on guinea pigs, rabbits and cats by applying solutions of powerful pharmacologic agents

to the prepuce and penis and observing the symptoms of systemic absorption (if there were any) and effects on various physiologic functions. The striking results obtained demonstrated that many drugs and poisons are readily absorbed through the male organs. These experiments will be described in detail in a journal devoted to genitourinary diseases. It will suffice to state here that the writer found that rapid absorption followed such application of the antiseptics phenol and cresol, of nitroglycerin, of the alkaloids atropine, strychnine, aconitine and nicotine, of the volatile oils and also of cobra venom. Thus the rapid absorption of aconitine or a minute quantity of nicotine alkaloid, applied in this way, was demonstrated by the characteristic effects on the respiration and blood pressure curves traced on a kymograph. Such administration of these powerful poisons was followed by death in a few minutes. Applications of strychnine to guinea pigs elicited typical convulsions. Similar use of atropine and pilocarpine was succeeded by the characteristic pharmacologic effect, indicating their absorption into the circulation.

It was more difficult to determine whether or not menstrual toxin may be absorbed through the male genitalia. Experiments were made on rabbits and cats under general anesthesia. In such animals the effect of normal human blood serum introduced into the preputial sac was compared with that of menstrual blood serum similarly administered. In some of these tests, but not in all, it was found that menstrual serum differed from the control in its effect on the blood pressure. The menotoxic serum effected a definite rise in blood pressure while normal serum had little or no effect on the curve (see Fig. 4). While it cannot be stated with absolute certainty that the rise in blood pressure was due to absorption and the consequent vasoconstricting effect of menotoxin, this may be assumed in view of Labhardt and Hüssy's[65] studies on the vasoconstricting property of menotoxin on peripheral vessels.

To ascertain more definitely whether the absorption of blood serum in general may be accomplished by its local application to the prepuce or penis, the writer resorted to a new and very delicate biologic test, of immunologic character. Some years ago it was demonstrated that guinea pigs may be sensitized to horse serum[71k] and other proteins[71l] applied to the mucous membrane of the vagina. Such guinea pigs, treated locally with horse serum for several days and allowed to rest for a period of 2 to 3 weeks, developed typical anaphylactic or allergic phenomena when injected with a dose of the antigen after the rest interval. A similar procedure was employed in the present investigation. For 5 days male guinea pigs of various sizes were sensitized by daily applications of 0.2 cc. of horse serum to the prepuce or phallus. They were then allowed to rest for 2 or 3 weeks after which 1 cc. of horse serum was injected into the circulation of each. The marked allergic reactions elicited by such injections were identically like those exhibited by control guinea pigs sensitized 3 weeks before by single *subcutaneous* injections of horse serum. On the other hand, after large doses of the antigen had been injected directly into the circulation of

each of another series of control guinea pigs, not previously injected with horse serum, no allergic symptom, much less anaphylactic shock was noted.

In the present study experiments were made with a series of 30 guinea pigs. Of 10 which had been sensitized by subcutaneous injection of horse serum, all developed severe anaphylactic shock and 8 died. Ten other guinea pigs were sensitized by application of horse serum to the male genitalia. Later, when the antigen was injected directly into the
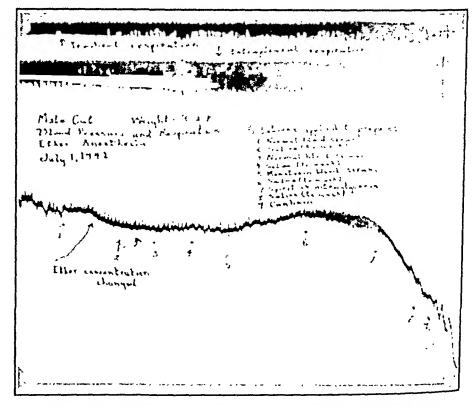
Fig. 4. Effect produced on blood pressure and respiration by various substances applied to the prepuce of male cat under ether anesthesia. Note, at 5, the negative effect of application of normal human blood serum; at 6, the pressor action effected by menstrual blood serum; at 7, the marked fall in blood pressure induced by application of dilute spirits of nitroglycerin; and, at 9, the lethal effect of ouabain.

circulation, they developed violent anaphylactic shock. Seven of these animals died in from 5 to 10 minutes, while 2 exhibiting typical allergic reactions and 1 but mild allergic reactions subsequently recovered. Horse serum was injected directly into the circulation of the 10 guinea pigs remaining in the series, which were used as controls, and none of them displayed any sign of allergic reaction or anaphylactic shock. The anaphylactic shock developed in the guinea pigs treated with applications of the antigen to the genitalia was striking and characteristic. On its injection into the circulation of the respective

guinea pigs, they first became restless, then rubbed their noses and made clucking noises suggestive of respiratory obstruction. Auscultation of such animals with a stethoscope revealed marked bronchial constriction and squeaking râles. The animals began to tremble and shiver, then developed more or less violent convulsions, fell over on the side prostrated, passed into a comatose state and died. Post-mortem examination usually revealed greatly distended lungs with constricted bronchi.

Such experiments as those described above are conclusive proof that sufficient blood serum can be absorbed through the prepuce or surface of the penis to sensitize the animals. If that is the case with normal blood serum, it may be assumed that similar absorption would follow applications of menstrual serum to the same organs; and if such a serum has a toxic property not exhibited by normal serum, it may be expected that it will exert a harmful effect on the animals. In addition, experiments were made on previously circumcised guinea pigs. Sensitization in these animals was also achieved by local applications of horse serum but the reactions after injection of the antigen were not quite so violent and suggested that absorption through the cornified integument was slower than it was through the mucous membranes of the uncircumcised animals.

It is interesting to note that historical and ethnologic studies inform us that among most peoples of ancient times as well as of the present day, cohabitation of husband and wife at time of catamenia is discouraged for either hygienic or esthetic reasons. Among the older nations we even find religious prohibitions to that effect, and every Bible student knows that the Old Testament enjoins complete separation of husband and wife not only during the period of actual catamenia but for 7 days after cessation of the flow. This empirical injunction is in obvious conformity with the findings made in the researches described above. Furthermore, we may observe that the ancient custom is in complete accord with the latest embryologic and endocrinologic teachings concerning the relation between menstruation and ovulation.[99b] The two physiologic processes are not synchronous. On the contrary, we now know that ovulation and fertilization of the ovum cannot take place at the time of catamenia and is accomplished in the intermenstrual interval. It appears therefore that the Hebrew prohibitions concerning menstruation have a sound embryologic and physiologic basis,[122] for the primary purpose of marriage according to all civilized religions is the propagation of the species.

Review of Experimental Literature. In order to examine more intelligently and critically the mass of folklore which has accumulated concerning menstruation and to secure a scientific basis for study of the periodic spells of malaise and illness from which women suffer, let us review the experimental evidence which has been amassed regarding the toxin of catamenia. In this way we shall sift the chaff from the wheat and discover the modicum of truth beneath the crust of myth, magic, poetry and superstition, and thus make a rational approach to the clinical problems involved in the subject. The experimental evi-

dence on menotoxin may be classified as: (1) botanical, (2) zoöpharmacologic, (3) psychologic, (4) physical and (5) chemical.

1. *Botanical Experiments.* The earliest work on effect of menotoxin may be dated from the investigation Bela Schick carried out on cut flowers. Such tests on flowers, also made by Macht and Lubin, by Frank,[5] Sanger[115] and others, cannot *per se* be regarded as conclusive scientific evidence of a menotoxin but they were corroborated by the more quantitative and controlled experimentation attempted later and they also served to enlist the interest of the medical world in the possibility of the existence of a menstrual toxin. The evidence derived from the tests made on cut flowers was inconclusive by reason of the inadequate methods employed for such study. Schick's tests on cut flowers might be roughly compared with experiments physiologists might undertake on decerebrated animals without ligating the blood vessels to maintain the circulation or making any provision for keeping the respiratory function intact. Experiments on cut flowers without proper plant-physiologic technique may be compared, too, to studies on surviving isolated animal tissues suspended in water instead of warm oxygenated physiologic saline solution. Quantitative plant-physiologic work on menotoxin may be dated from the experiments of Macht and Lubin on intact seedlings grown in plant-physiologic solutions of different chemical composition under standardized ecologic conditions. Employing such a method these authors demonstrated conclusively the presence of a toxic substance in the blood, saliva, tears, sweat, milk, urine and other secretions of women at catamenia, a toxin not found in the blood and other secretions of the same individuals during the intermenstrual period. Macht and Grumbein[74] demonstrated the presence of this toxin even in dry and frozen blood specimens, and Böhmer[11] duplicated their research on dry blood with a view to proving its usefulness for diagnostic purposes in forensic cases. But the studies of Macht and Lubin on root growth of *Lupinus albus* seedlings did not supply the only botanical proof they obtained of the existence of a toxin in menstrual blood and secretions. These authors have shown that menstrual serum, as compared with controls of normal human blood, exerted a toxic action on protoplasmic streaming, on germination of seeds, on growth of flowers and stems, on the geotropic functions of higher plants and on the respiration and transpiration phenomena of leaves. For practical purposes, however, the study on root growth of *Lupinus albus* seedlings has remained the most convenient method for quantitative study of the toxicity of menstrual blood, and the writer and his associates have found the phytopharmacologic method originally employed for this purpose equally useful for the detection of minute quantities of other toxins in several important clinical conditions.[77] Thus the phytopharmacologic method demonstrated the presence of a toxin in the blood of pernicious anemia,[70,5,72] which is not found in other forms of anemia, namely, those due to malignant disease, tuberculosis, leukemia, and so forth. Similarly a toxin was discovered in the blood of leprosy,[71m] and an extensive investigation carried on by Macht and Pels furnished the first experimental

proof of the presence of a toxin in the blood of pemphigus.[86,103a,103b] Employing the phytopharmacologic method, the Russian pharmacologist Tscherkes was the first to call attention to the toxin of trachoma.[71o] Later his findings were confirmed by Macht on blood sera obtained from North American Indians suffering from the same disease.[71p] Further search for toxic substances specific for special diseases is now in progress in this laboratory. An important phase of such experimentation is that undertaken with blood sera from different types of psychoses.[84] A detailed description of all these findings does not fall within the scope of the present paper but it may be asserted that, having weathered 20 years of testing and criticism, the phytopharmacologic technique in competent hands yields quantitative experimental data proving reliable on statistical analyses[83] and often more dependable than the data obtained by zoöpharmacologic tests because of the inherent restrictions as to the number of available animals in an ordinary pharmacologic laboratory.

The use of living seedlings for the study of menstrual toxin seems to have received fresh stimulus since 1932, the approximate date on which newer phytopharmacologic as well as zoöpharmacologic studies on the subject were announced by Macht and Davis before the Section on Psychology of the American Association for the Advancement of Science. It is curious that some of the most scholarly researches on the subject have been conducted by pediatricians interested in investigating that toxicity of mother's milk during menstruation which was first demonstrated by Macht and Lubin. It is a well-established empirical observation among general practitioners as well as nursing mothers, and others, that human milk at catamenia is liable to upset the gastro-intestinal system of nursing infants. Accordingly, the matter was submitted to experimental study. Of special interest is the work of Fraenkel,[38] Silber,[124] Eltz,[31] Borsarelli,[13] Steinert and Papp[128] on the toxicity of human milk at catamenia by the phytopharmacologic method. Among the work published on this subject were the researches of Eltz and Mommsen,[95] who not only demonstrated the toxicity of menstrual milk for living seedlings but succeeded in obtaining toxic blood serum from rabbits fed with such milk.

A number of investigators have studied the effects of menstrual toxin on yeasts and bacteria. Macht and Hill have already reported experiments regarding the inhibitory action of menstrual serum, as compared with normal serum, on cultures of *B. coli*. Sutterlin and Szelinski[129] studied the effect of menstrual toxin on the keeping qualities of food. Christiansen[20] studied the toxic action of menstrual blood on *Lactobacillus bulgaricus*. Polano and Dietl[106] denied that menstrual toxin inhibited growth of yeast cells but their work has been controverted by numerous other experimenters who agree as to the toxic action of this substance on reproduction of yeasts and other fungi. Rahn[6,110] and his co-worker published elaborate quantitative studies concerning the inhibitory action of menotoxin on *Saccharomyces mycoderma*. Mommsen reported elaborate studies not only on poisonous effect of menotoxin on yeasts but also on the chemical nature of this toxic

substance, studies which refuted the so-called acetyl-choline theory concerning its structure. Böhmer showed that solutions of dry menstrual blood were toxic for yeasts as well as other plant-physiologic test objects, whereas the dry blood from control subjects exerted no such inhibitory action. Borsarelli found that menstrual toxin is toxic for the fungus *Aspergillus niger*. In this connection the empirical observations of a British physician, Burgess,[1] dating as far back as 1878, are of special interest. "It is a fact generally known to every housewife and cook that meat would spoil if salted at the menstrual period" and "It is undoubtedly the fact that meat will be tainted if cured by women at the catamenial period, and that hog meat will not cure or take salt when the rubber is menstruating."

2. *Zoöpharmacologic Experiments.* In the study of blood toxins in general and of menstrual toxin in particular, the phytopharmacologic technique yields more specific and hence more impressive results than zoöpharmacologic methods. Generally speaking, it has been found that substances toxic enough to injure living plants occur in the blood of but few pathologic conditions, which does not mean that menstrual toxin has no harmful effect on animal test objects, although it is not so specific and its action can be duplicated by many other poisons. Macht and Lubin found that menstrual serum is more toxic than normal blood for goldfish and paramecia. Macht and Davis reported other zoöpharmacologic findings. Menotoxin was found to effect such sensitization of vasa deferentia of rats as to make them abnormally responsive to treatment with epinephrine and ephedrine, a sensitization not unlike that Ascher noted after treatment of smooth muscle organs with thyroxin. Lanczos[69] studied the effect of menstrual poison on gastrocnemius preparations. Macht and Elvers[35] observed its action on living spermatozoa. Borsarelli found menstrual serum exceedingly poisonous for larvae of *Bufo vulgaris*. Macht and Davis noted the toxicity of menstrual serum for rats, Smith and Smith later confirming and extending this finding. Strangely enough, Macht found that menstrual blood is less poisonous for mice than for rats but Levinson[65] discovered that it is very toxic for guinea pigs. Labhardt[64] and Hüssy[65] found that, as compared with normal blood, menstrual blood is rich in vasoconstricting substances which could be demonstrated by perfusion experiments and tests on surviving muscle preparations. Patzschke and Sieburg found that the sweat of menstruating women, as compared with that of the same individuals during the intermenstrual period, stimulated contractions of intestinal and other smooth muscle preparations. The present writer has already described the vasoconstricting effect of local application of menstrual serum to genitalia of male cats and rabbits. Eltz and Mommsen demonstrated the toxicity of blood of rabbits fed with menstrual milk. Psychologic experiments will be described below. Special mention, however, should be made of the work of various scientists on the coagulation of blood. Barthelmez's[7] review of the subject contains a complete résumé of these findings. Studies have been made in particular by Zondek,[147] Kross,[63] Dogliotti[27] and Macht.[71b] All these investigators found that the coagulability of

menstrual blood differs from that of normal blood, the majority claiming that coagulation is delayed during catamenia.

3. *Psychologic Experiments.* It is a time-honored tradition that women at the time of their periods are "unwell," particularly in the psychologic sense of the word. Depression, as well as other nervous ailments, at that time are very common, but no experimental psychologic work of conclusive character has been published on the subject until recently. An objective experimental study on animals was first undertaken by Macht and Hyndman who studied the effects of normal and menstrual blood, respectively, on the behavior of albino rats in the circular maze. This research was repeated and extended by Macht and Davis. In the current study the psychologic experimentation already described has been carried on along three different lines of research. All the data yielded by such tests indicated that injections of menstrual blood sera profoundly affect the neuromuscular system of albino rats, and conform with the results of clinical studies made by various gynecologists and psychiatrists. Thus Tuttle[135] made a statistical study of the irritability of women during the menstrual cycle.

4. *Physical Experiments.* These have been concerned chiefly with radiologic studies. The subject of menstrual toxins is so intimately connected with numerous superstitions, folklore and taboos that the average investigator is inclined to lose his poise and impartial attitude when studying current experimental findings and to frown upon the work of the most reputable researchers. With this preliminary comment the writer proceeds to describe the remarkable experiments reported by Christiansen and by Rahn[109] and his associates, Barnes and Ferguson.[35] Interested in mitogenetic rays and the radiations given off by living cells, particularly of the human body, these investigators have reported the results of their quantitative experiments on yeasts. In a paper entitled "Das Menotoxinproblem und die mitogenetischen Strahlen," Christiansen showed that proliferation of yeast cells can be inhibited by emanations or radiations from the bodies of menstruating women having no other contact with the yeast cells. Rahn and Barnes and Ferguson published detailed reports of such studies, carried out on a larger scale. The Rahn school found that certain radiations of the human body, especially at catamenia, and occasionally also in course of certain diseases, definitely inhibited the growth of yeasts. Various parts of the body, such as the fingertips, and even the eyes were said to give off these radiations. The present writer did not succeed in confirming these findings phytopharmacologically; however, Rahn and his associates admit that there are wide individual variations with regard to lethal dosage, some giving off more emanations than others. The subject must be left *sub judice*, and the writer confines himself merely to quoting the statement of Rahn and Barnes published in 1933: "The old 'superstition' that menstruating women cause flowers to wilt and fermentations to become abnormal has been verified experimentally by several authors. In 1929, Christensen proved that menstrual blood will kill yeast cells, or change them morphologically, even through a quartz coverglass.

"The authors observed that this influence is not limited to menstruating women. One woman could not obtain growth of a very sensitive species of yeast for periods of 10 to 20 days, alternating with periods of normal growth. Radiation from her fingertips through a quartz plate killed the yeast in 15 minutes. One man killed yeast by this method in half of all tests. Even his eye and nose, at very close range through quartz, had the same effect. Since this radiation does not pass through glass slides, it is probably ultraviolet.

"Observations for more than one year suggest that this radiation is due to pathological conditions. Both the above cases can be explained in this way, and there are other similar observations.

"Macht and Lubin have shown the menstrual toxin to be identical with or closely related to oxycholesterol. We observed this compound to kill yeast through quartz. So did the ether washings from the fingers of menstruating persons. This kind of radiation may therefore be explained simply by a pathological excretion of oxycholesterol through the skin."

Here we may mention also the interesting work of Burr and Musselman[17] on the bioelectric correlates of the menstrual cycle, a research which does not deal with such ultraviolet radiations as engaged the attention of Rahn and his co-workers but with electric potentials in women before and during menstruation. These investigators found that the electric potential difference rises significantly during the days immediately following the menstrual period. There appears to be some connection between the menstrual cycle and certain electric potentials of the body tissues.

5. *Chemical Experiments.* While the chemical nature of menstrual poison is not yet completely understood and crystalline or chemically pure menotoxin has not yet been isolated, the experimental, pharmacologic and biochemical work already done throws considerable light on this subject. Labhardt and Hüssy concluded from their biologic experiments that menotoxin is a vasoconstricting substance. Sieburg and Patzschke,[123] Klaus[62] and others believed this toxin to be closely related to, if not identical with, choline. The phytopharmacologic findings of Macht and his collaborators contradict this hypothesis for they found that choline and acetyl-choline are not toxic for plant protoplasm. Ashley Montagu[96] believes this toxin to be identical with di-methyl-amine, a substance discovered, many years before, by Michin.[91] Macaggi and Sivori[70] regard it as closely related to thyroxin or the active principle of the thyroid gland. The curious findings obtained by Macht and Davis in their studies with menotoxin on the irritability of the vas deferens lend support to the latter view. Gautier[41] and Bourcet[14] also incline to the opinion that there is a chemical link between the arsenic and iodine content of the thyroid gland and the menstrual cycle. Steinert and Papp attribute the toxicity of human menstrual milk to a reduction in diastatic ferments. None of these hypotheses is supported by decisive chemical data and the majority of physiologic proofs adduced in their favor would not withstand a critical phytopharmacologic test, which seems to be more specific than

the zoöpharmacologic method in detecting menstrual toxin. The original findings of Macht and Lubin, based on such pharmacologic and biochemical experimentation, appear to indicate a closer relationship of menotoxin and cholesterin or, more strictly speaking, oxycholesterin, in chemical composition. Thus it was discovered that wherever found in the human body, whether in the skin fat or in the vernix caseosa or elsewhere, even weak solutions of oxycholesterin in plant-physiologic media markedly inhibited the growth of *Lupinus albus* seedlings. Unna and Golodetz[136] have shown that the human skin is rich in fats containing considerable quantities of cholesterol and cholesterol derivatives. Furthermore comedones and sebaceous glands of the face and fingernails have proved to be rich in cholesterol derivatives. Phytopharmacologic experiments performed by the writer revealed that extracts of all these were toxic for *Lupinus albus* seedlings. Other poisons of animal origin, such as the toad poison, *bufagin*, of Abel and Macht,[1] had been found by the latter to be very poisonous for plant growth. This toad poison, as well as others later studied by Chen,[19] are all derivatives of cholesterol. Perhaps the most striking single experimental proof supporting the original oxycholesterol theory was the finding by Rahn that inhibitory effects on yeast similar to those he had observed in his radiologic tests on menstruating women were produced by cholesterol itself. Further support is lent the cholesterol or oxycholesterol hypothesis by the fact that recent chemical studies on the structure of the sex hormones in general and of ovarian hormones in particular have disclosed their intimate relationship in chemical structure to cholesterin.[36] The findings made by Macht and his associates on the interrelation of menotoxin and bile salts also support this view.[79b] It is remarkable that such divergent substances as the carcinogenic chemicals, the digitaloid drugs, including toad poisons, the sex hormones, the group of vitamin D compounds and menotoxin are all derivatives of the phenanthrene nucleus and closely related to cholesterol.

Popular and Empirical Observations. The student of medical history will be amazed at the light shed by these accumulated experimental findings—botanical, zoölogic, psychologic, radiologic and chemical—on the numerous popular beliefs and taboos of the laity and empirical observations of the older physicians and naturalists concerning menstrual phenomena. Most of these empirical observations have a rational substratum. The wilting of flowers by the touch of menstruating women is a fact familiar to the majority of the sex the world over and what has long been styled superstition is now well attested by experimental scientific data. Even such extravagant remarks as those found in the writings of the elder Pliny[104] concerning the poison of menstruation and its contamination of seeds, garden plants, leaves and so forth, are now found to be not so far from truth as many pseudoscientists would like to have it appear in their endeavor to disparage the keen observations of the older naturalists. The spoiling of such foods as fruit, vegetables and cucumbers and cabbages handled by menstruating women may be satisfactorily explained by the pharma-

cologic findings made concerning the effects of menotoxin on yeast, fungi and lower organisms. Similarly there appears to be some physical basis for the legal or systematic regulation in various industries prohibiting women who are menstruating from engaging in the manufacture of perfumes, tending of silkworms, gathering of mushrooms and expressing of grapes for the making of wine. The old British physician was correct in his inference that the curing of meats might not be successfully effected if they were handled by menstruating women. So we may also regard as needful the old Russian custom of discouraging the pickling of cucumbers or preparation of cabbage for sauerkraut by such individuals. In the light of the experimental findings of Macht and Lubin and also of pediatricians, we can now stress the fact that dough kneaded by menstruating women is liable to result in lumpy and poorly risen bread. A number of other popular observations concerning the poison of menstruation may be cited in this connection. The Frenchman, Laurent,[6] and the Englishman, Ellis,[22] tell us that in France women who are unwell are not admitted into those departments of sugar refineries in which the syrup is boiling and sugar is being bleached because it is believed that their touch would discolor the product. The same Laurent relates that in the Far East, menstruating women are not allowed to pick poppyheads and prepare opium because of the inferior product which would result. Were it not for the remarkable radiologic data published by Christiansen, Rahn, Barnes and Ferguson, the writer would refrain from quoting Laurent with regard to another and singular clinical observation. He described a series of cases of women musicians obliged to discontinue use of their stringed instruments during the menstrual period because of the effect of their touch on violins, violas, cellos and harps. The strings, it was said, did not emit the proper tone when manipulated by menstruating women and often snapped in the midst of their performance. While this last bit of narrative must be considered with reservation, it may be admitted that on the whole certain ludicrous aspects of some of the old taboos have possibly been exaggerated due to the superiority complex of certain professional modernistic folklorists with not sufficient insight to determine their origin. In the writer's opinion the remarks repeated above are not a whit more fantastic than the fatuous balderdash of such Freudian extremists as Gerson[42] or the maudlin vaporings of such professional mystical interpretations as emanate from Harding,[31] who writes on the man in the moon and the moon cycle of women as an astrologic phenomenon. The true scientist, who does not dwell on beliefs or unbeliefs but seeks for facts and truth, will certainly meditate on the extraordinary concordance of the Biblical account regarding menstruation and the phytopharmacologic and other experimental data on the subject accumulated in this paper. It may be well to add that even the puzzling references to postpuerperal phenomena in Leviticus XIII have also been found to have some basis in the findings of Macht and Leach[80] concerning the toxicity of puerperal bloods.

Interrelation of Menstruation and Various Physiologic and Pathologic Conditions. To assert that the menses affect a woman's well-being is

to state a platitude for the very expression "unwell" is universally descriptive of women at catamenia and implies a pathologic state of the individual. The profound physiologic changes occurring in the generative organs during the menses may also affect every other function of the female body. As modern physiology has developed, it has been found that numerous changes in functions of all the organs or parts of the female body, whether normal or diseased, run parallel with the menstrual cycle. Such studies were made over 70 years ago by the old authorities. Thus Schäffer[118] found that 74% of 220 healthy women complained of various subjective symptoms during their periods and 14% of these suffered to a pathologic degree. Similar studies were made by Töbler,[133] Rabuteau,[108] Goodmann,[43] Jacobi,[57] and others who stressed the wavelike change in metabolism and other functions which followed a course running parallel to the menstrual cycle. A host of later observers studied other physiologic phenomena in relation to menstruation. Kersh[60] and Reinl[111] measured the temperature. Ver Eecke[137] determined the output of urea, phosphates and chlorides; Wiessner,[143] Merletti,[93] Siredey,[125] and Francillion[39] noted the regularly recurring peaks and depressions in blood pressure which accompanied the menstrual period, and von Ott[102] published a significant work with graphs showing the intimate relation of fluctuations in temperature, pulse, blood pressure, lung capacity and various reflexes to the menses. Schräder[121] made biochemical studies on nitrogen elimination at that time. The newer literature on the interrelation of the menstrual cycle and women's normal physiologic functions is conveniently tabulated in Fluhmann's admirable monograph on "Menstrual Disorders."[37] Thus we find that a periodic rise in temperature has been observed by Cullis,[23] Jacoby,[58] and Rubenstein.[114] Such regularly recurring changes in blood pressure as have been reported by older clinicians have been confirmed by the work of Amos,[3] Griffith,[47] and Moore and Jenkins,[97] employing newer methods. Alterations in the pulse rate during the menses have been described by Truesdell and Croxford.[134] Quantitative biochemical studies on calcium content were made by Bock,[10] on potassium content by Spiegler,[127] on arsenic content by Guthmann and Grass,[49] on cholesterol content by Okey and Boyden[100] and Guillaumin and Vignes,[48] and on iodine content by Maurer,[91] and Scheringer,[119] and Hermstein.[53] Changes in the circulatory blood during menstruation have been followed by Holler, Melicher and Reiter,[56] and also by Dietre.[121] Hirsch and Hartmann[55] observed periodic increase in blood platelets during the menses while Eufinger[33] and Tedstrom and Wilson[131] noted regularly recurring fluctuations in the blood sugar irrespective of the diet. Changes in basal metabolism in relation to monthly periods have been studied by Benedict and Finn,[8] and also by Wakeham[139] and Wible.[142]

With regard to the relation between menstruation and various pathologic conditions, it is not surprising to find that even more striking changes have been observed by clinicians and correlated with the menstrual cycle as cause and effect. The course of various diseases may be influenced by the onset of catamenia and, conversely, many

maladies exert a marked effect on menstruation, some inducing menorrhagia and others amenorrhea. Interrelation of the menstrual cycle and various diseases was discussed 15 years ago by Aschner,[2] the eminent Viennese gynecologist, who inclined even then to the view that many pathologic conditions during catamenia may be precipitated or exaggerated by retention of menstrual toxin. A more recent account of the various diseases which may affect the menstrual cycle or which, conversely, may be affected by onset or suppression of menstruation will be found in the monograph of Emil Novak.[9a]

A host of pathologic symptoms and physiologic disturbances may either be precipitated or aggravated during the menses. Among the more important are the following:

1. *Disturbances of Neurologic and Psychologic Character.* These are among the commonest and range from the mildest forms of hyperirritability through the phobias, anxiety neuroses and depression to melancholia, mania and dementia praecox. Mary Chadwick,[18] in her monograph on "Psychological Effects of Menstruation," proposes that these psychologic disturbances in women at catamenia were the origin of the ancient prohibitions and limitations which later developed into all kinds of taboos. The insomnia, various types of psychologic neuroses and hysteria from which some women suffer periodically bear some relation to the menses. Epileptiform seizures are of greater violence or recur only at that time. Such studies on epilepsy have been made by Alexander,[2] Davidson,[24] and Gordon,[40] and Diepgen and Schröder[25] have investigated hysteria in relation to the menses. Various psychotic aspects of the subject have been investigated by Haymann,[52] MacKenzie,[39] Ross,[112] and Swanberg.[120] A case of acute insanity occurring regularly at catamenia has been described by the present writer.[71b]

2. *Headache.* Headache, often hemicranial, is a special form of neurosis which Aschner regards as an evidence of menstrual toxicosis. Scattered references to this symptom are found in the literature and a discussion of it appeared recently in the *Journal of the American Medical Association.*[107]

3. *Dermatoses.* Such manifestations are among the commonest noted in connection with catamenia. These skin lesions include furunculosis, acne, rosacea, herpes labialis, herpes zoster, urticaria, various forms of eczema, subcutaneous hemorrhage, erythema multiforme, erythema nodosum and localized patches of edema. Macht and Pels in their phytopharmacologic study of bloods from all kinds of dermatoses noted that the menstrual sera of women suffering from acne were generally more toxic than such sera from those who did not have acne. On the other hand, blood specimens from young men with widespread acne rarely exerted a phytotoxic reaction. Numerous dermatologic manifestations related to the menstrual period have been studied by Jerusalem,[59] Opel,[101] Edebohls[29] and others whose work is conveniently summarized in Novak's monograph.

4. *Ophthalmic Manifestations.* The laity have noted such symptoms from remotest antiquity and the baleful look of menstruating women receives frequent mention in the folklore. Organic disturbances

of the visual apparatus often occurring at catamenia include conjunctivitis, scleritis, iritis, herpes corneæ and retinitis, choroiditis and even detachment of the retina. Important contributions on the subject have been made by Dunn,[28] Greeff,[46] and Napier,[98] the last two authors writing on dysmenorrhea and amenorrhea.

5. *Arthralgias and Neuralgias.* All types of arthralgia and neuralgia are complained of during catamenia and may be precipitated periodically or may be exacerbated by onset of the menses. Aschner stated that of 700 patients whom he studied no less than 230 complained of varying degrees of arthritis and neuralgia. Some suffered from sciatica; others had inflammatory infections of the joints; and still others complained of lumbago and myalgias. All these ailments he attributed to excessive accumulation of menstrual poison in the system of menstruating women. More recently Rugh[115] described a series of arthritic cases which he also explained on the basis of the retention of the menotoxin in the system of his patients.

6. *Gastro-intestinal Manifestations.* Though usually of a mild character such manifestations may occasionally be of the more serious type described by Brush[15] and Plönies.[105]

7. *Hepatic and Cholecystic Manifestations.* These have also been noted during the menstrual period. Thus hyperemia and swelling of the liver have been described by Chvostek[21] and Fellner.[34] Periodic jaundice is mentioned by the famous German internist, Senator,[117] and gall bladder attacks in relation to the menses have been described by Binet.[9]

8. *Vasomotor and Other Disturbances of the Circulation.* Such manifestations during the periods have been described by Kisch,[61] Williams[144] and others.

9. *Thyroid Manifestations.* Mild periodic manifestations on the part of the thyroid gland are not uncommon during the menses but sometimes even the more serious forms of the disease, *i. e.,* exophthalmic goitre, are profoundly affected by the menstrual cycle. Studies on this subject have been published by Thoma,[132] Wallin,[141] and Woronytsch.[146]

10. *Respiratory Manifestations.* The respiratory organs have also been found to suffer in the course of menstrual abnormalities. All sorts of catarrhal conditions have been noted at catamenia. Asthmatic attacks have frequently been aggravated by onset of menstruation.

11. *Acute Infections.* Periodic menstrual manifestations of pathologic character have been observed in the course of various acute infections. Thus influenza has been studied in this respect by Osler and McCrae[102] and typhoid and pneumonia by Rosenstraus[112] and Esch.[32]

12. *Syphilitic Infections.* Of the chronic infections studied in relation to the monthly periods, syphilis has received the attention of Meirowsky.[92]

13. *Tuberculous Manifestations.* The most important chronic disease influenced by the menses and exerting a profound effect on the menstrual cycle is tuberculosis. Macht[71] studied this subject extensively in 1910 and it has also been investigated by Handford,[50] Gräfen-

burg[15] and others. There can be no doubt about the flaring up of acute symptoms in tuberculous patients at any time as manifested by rise in temperature, pulmonary hemorrhages and other pathological phenomena. The present writer noted a curious case of periodic intestinal hemorrhage in a patient with intestinal tuberculosis.[31a] The influence of chronic tuberculosis on the menstrual cycle has also been widely studied. In its early stages the disease may manifest itself by a menorrhagia whereas later it is usually accompanied by amenorrhea or complete suppression of the menses.

14. *Miscellaneous Manifestations.* Clinical investigators have correlated various other forms of pathologic disturbance with the menstrual cycle. These all attest the profound influence which the ovulatory cycle and catamenia exert upon practically every physiologic function of women. The cause of this periodic fluctuation in normal physiologic functions, including metabolism, and other pathologic symptoms appearing at the height of the menstrual period has engaged the attention of numerous students of medicine and is discussed below.

Discussion. A judicious and scientific appraisal of the experimental and clinical data presented in this paper justifies us in drawing several fairly definite conclusions. In the first place, the biologic experimental data demonstrate beyond reasonable doubt the presence in the blood and secretions of menstruating women of a toxic substance normally absent. Whether this substance be called toxin or abnormal product of metabolism or degradation product of an endocrine secretion is immaterial. Second, such a "menotoxin" provides a physical explanation of many curious popular beliefs and empirical observations of laymen handed down from remote antiquity. Third, abundant clinical evidence points to a periodic fluctuation in normal physiologic processes of women which runs parallel to the menstrual cycle. Fourth, numerous clinical observations have established the fact that many pathologic symptoms and objective signs of disease are correlated with the course of menstruation and abnormalities in the menstrual cycle. Two schools of investigators have tried to explain these pathologic manifestations, one of these, well represented by Aschner, asserting that the menstrual toxin plays the chief rôle in this connection, and the other, composed of many enthusiastic endocrinologists, contending that the female sex hormones cause most gynecologic ailments. Aschner's view gains some support from the fact that patients undergoing hysterectomy, even without removal of the ovaries, exhibit pathologic symptoms not attributable to lack of ovarian secretions and which may more logically be ascribed to chronic intoxication due to failure to excrete some toxic substance through the normal genital routes. The same is true of cases with ovarian transplants and substitution therapy. Aschner cites many cases of amenorrhea and scanty menstruation favoring the assumption that a menotoxin is thus retained by such patients. The symptoms observed in such cases are not unlike those noted in connection with dysfunction of and defective elimination of noxious products from other organs as in chronic dyspepsia,

constipation, impaired kidney function or secretion of the glands. Aschner claims that endocrine therapy in such cases is of no avail, while therapy aimed at promoting elimination of toxins and excretion of abnormal metabolic products often relieves the patients' sufferings. Although recent developments in the study of internal secretions have led to important discoveries, the therapeutic use of endocrines has not been remarkably fortunate, particularly in the field of sex hormones.

While all scientific investigation compels us to beware of drawing hasty, illogical conclusions and particularly of succumbing to the fallacy of *post hoc propter hoc*, the astonishing parallelism (revealed by newer quantitative pharmacologic measures), beginning a day or two before catamenia and reaching its peak at beginning of the flow, between menstrual toxemia and the exacerbations and remissions of clinical symptomatology and pathology, suggests a causal relation between the two phenomena. Results of the latest clinical studies can be best explained in this way. Thus Conn[22] describes a female patient with aggressive psychopathic personality who had exaggerated manifestations in the premenstrual period. The present writer also is acquainted with a case in which a young woman with psychopersonality shows extreme emotional instability and affective psychoses at that time. These acute exacerbations of mental phenomena conform with the phytopharmacologic findings Macht has made in such cases. Again, Waldbott and Bailey[140] have recently published a paper on estrogenic hormone determinations in premenstrual asthma, from which the impartial reader cannot discover whether the asthmatic attacks bore any relation to the hormone determinations or even that the endocrine injections definitely relieved the allergic symptoms.

The present writer holds that the distinction between the two views is largely academic and that the menstrual toxin and ovarian hormones are more closely related than has been assumed. In the female organism there is a periodic accumulation, under the influence of ovarian secretions, of certain substances essential to furtherance of fertilization and implantation of the ovum. Failure of this excretion, usually controlled by the menstrual flow, leads not only to retention of the poisons but to many pathologic symptoms. Recent chemical studies support this view for the findings of the present writer and his associates regarding the chemical structure of menotoxin and those of Rahn, Barnes, Ferguson and other investigators indicate its probable close relationship to oxycholesterol. It is now known that the ovarian hormones also are closely related to that substance, the investigations of Mandelshtam, Tschaikowsky and Bondarenko supplying further evidence[90] in this connection. Studying the chemical nature of menotoxin by phytopharmacologic methods, these investigators also experimented on the effect of folliculin and the lipoid portions of the ovaries on plant growth and concluded that menstrual poison is closely related to the ovarian sex hormones. The present writer found that while crystalline estrone solution has a tendency to stimulate root growth of *Lupinus albus* seedlings, crystalline progesterone definitely inhibits it.[74] The findings of Macht and his associates on the interrelation of meno-

toxin and bile salts also tend to support the view that menotoxin is closely allied to cholesterol. It is remarkable that such divergent substances as the carcinogenic chemicals, digitaloid drugs, toad poisons, sex hormones, ergosterol, calciferols and the group of compounds included under vitamin D, and menotoxin are all closely related chemically. All these are derivatives of phenanthrene and possess a structure not far removed from that of oxycholesterol. Such a relationship does not preclude the possibility of menotoxin's being much more toxic than the ovarian hormones as pharmacology abounds in striking examples of chemicals closely related in structure yet exhibiting diametrically opposite physiologic and toxicologic properties due to slight alterations in the relative position of some of their atoms.

Summary. 1. Experimental data demonstrate in the blood and secretions of menstruating women the presence of a toxic substance or menotoxin, which is poisonous for plants and animals.

2. This experimental biologic demonstration explains in large measure the numerous empirical observations on "menstrual poison" found in the folklore of many countries.

3. The interrelation of menstruation and various manifestations of disease is examined in the light of these findings.

4. Menotoxin has been found to be closely related pharmacologically to the phenanthrene derivatives, cholesterol and oxycholesterol; and, while it is a separate toxic entity, it is probably closely allied to the female sex hormones, which are also known to be natural products of phenanthrene and related in their structure to the sterols.

Addendum. After the above manuscript had gone to press, several additional items of interest appeared in the literature. Byrnes[17a] states that menstruating operators in certain industries stimulate corrosion of certain articles through contact with their perspiration. Hereford[52a] cites other instances of similar character. Basler[7a] by careful measurement found that the pull needed to epilate hairs was greater in the onset of catamenia than in the intermenstrual and the inefficiency of permanent hair wave manipulations at menses is discussed in a recent number of the *Journal of American Medical Association*.[107a]

The extraordinary concordance between recent findings about menstrual poison and the Biblical description on the subject gives support to the view that the Levitical ordinances concerning it, aside from their ethical, psychologic and religious significance, have a hygienic basis. In view of the newer advances in our knowledge concerning the chemical and biologic properties of water, the action of deuterium, of heavy water, and other isotopes, the specific characters of radioactive waters, the differences between ordinary and rain water, between natural and artificial sea water, etc., it would not be surprising to find a special hygienic significance in the elaborate ablutions recommended by the Scripture in connection with the postmenstrual purification rites.

REFERENCES

1. Abel, J. J., and Macht, D. I.: J. Pharmacol. and Exp. Ther., 3, 319, 1912.
2. Alexander, W.: Med. Press and Circ., 92, 600, 1911.
3. Amos, S. E.: Lancet, 2, 956, 1922.
4. Ascher, L., and Flack, M.: Ztschr. f. Biol., 55, 83, 1911.
5. Aschner, B.: Zentralbl. f. Gynäk., 51, 577, 1927.
6. Barnes, M. N., and Rahn, O.: Arch. f. Mikrobiol., 4, 583, 1933.
7. Barthelmez, G. W.: Physiol. Rev., 17, 28, 1937.
7a. Basler, A.: Med. Klin., 35, 111, 1939.
8. Benedict, F. G., and Finn, M. D.: Am. J. Physiol., 86, 59, 1928.
9. Binet, M. E.: Tribune Med., 41, 133, 1909.

10. Bock, A.: Monatschr. f. Geburtsh. u. Gynäk., **79**, 9, 1928.
11. Böhmer, K.: Deutsch. Ztschr. f. d. ges. gerichtl. Med., **10**, 430, 1927.
12. Boring, E. G., Langfeld, H. S., and Weld, H. P.: Introduction to Psychology, New York, 1939.
13. Borsarelli, F.: Riv. di clin. pediat., **31**, 189, 1933.
14. Bourcet, P.: Compt. rend. Acad. sc. Paris, **130**, 1721, 1900.
15. Brush, A. C.: J. Am. Med. Assn., **59**, 1777, 1912.
16. Burgess, R. E.: Brit. Med. J., **1**, 514, April 6; 541, Oct. 5, 1879.
17. Burr, H. S., and Musselman, L. K.: Am. J. Obst. and Gynec., **35**, 743, 1938.
17a. Byrnes, H. L.: Indust. Med., **10**, 80, 1941.
18. Chadwick, M.: The Psychological Effects of Menstruation, New York, 1932.
19. Chen, K. K., and Chen, A. L.: J. Pharmacol. and Exp. Ther., **49**, 503, 1933.
20. Christiansen, W.: Ber. d. deutsch. bot. Gesellsch., **47**, 357, 1929.
21. Chvostek, F.: Wien. klin. Wchnschr., **22**, 293, 1909.
22. Conn, J. H.: J. Nerv. and Ment. Dis., **95**, 316, 1942.
23. Cullis, W. C., Oppenheimer, E. M., and Ross–Johnson, M.: Lancet, **2**, 954, 1922.
24. Davidson, H. S.: Edinburgh Med. J., **4**, 125, 1910.
25. Diefgen, P., and Schröder, M.: Ztschr. f. klin. Med., **59**, 154, 1906.
26. Dietre, L.: Ztschr. f. d. ges. exp. Med., **59**, 240, 1928.
27. Dogliotti, V.: Folia gynæc., **29**, 119, 1932.
28. Dunn, J.: Arch. Ophthalmol., **24**, 353, 1895.
29. Edebohls, G. M.: New York J. Gynec. and Obst., **1**, 55, 1892.
30. Ellis, H.: Studies in the Psychology of Sex, Philadelphia, **1**, 1, 1902.
31. Eltz, E.: Jahrb. f. Kinderh., **136**, 82, 1932.
32. Esch, P.: Zentralbl. f. Gynäk., **43**, 161, 1919.
33. Eufinger, H.: Monatschr. f. Geburtsh. u. Gynäk., **93**, 51, 1932.
34. Fellner, D. O.: Med. Klin., **5**, 771, 1909.
35. Ferguson, A. J.: Morphological Changes in Yeast Induced by Biological Radiation, Diss., Cornell Univ., 1932.
36. Fieser, L. F.: Chemistry of Natural Products Related to Phenanthrene, Scranton, 1936.
37. Fluhmann, C. F.: Menstrual Disorders, Pathology, Diagnosis and Treatment, Philadelphia, 1939.
38. Fraenkel, L.: Beihefte z. med. Klin., **23**, 53, 1927.
39. Francillion, M.: La puberté chez la femme, Thèse de Paris, 1906.
40. Frank, M.: Monatschr. f. Kinderh., **21**, 474, 1921.
41. Gautier, A.: Compt. rend. Acad. sc. Paris, **131**, 361, 1900.
42. Gerson, A.: Ztschr. f. Sexwsch., **7**, 18, 1920.
43. Goodman, J.: Am. J. Obst. and Dis. of Women and Child., **11**, 673, 1878.
44. Gordon, A.: New York Med. J., **90**, 738, 1909.
45. Gräfenburg, E.: München. med. Wchnschr., **57**, 515, 1910.
46. Greeff, R.: Monatschr. f. Geburtsh. u. Gynäk., **3**, 425, 1896.
47. Griffith, F. R., et al.: Am. J. Physiol., **88**, 295, 1929.
48. Guillaumin, C. O., and Vignes, H.: Compt. rend. Soc. de biol., **99**, 753, 1928.
49. Guthmann, H., and Grass, H.: Arch. f. Gynäk., **152**, 127, 1932.
50. Handford, H.: Brit. Med. J., **1**, 153, 1887.
51. Harding, M. E.: Women's Mysteries, Ancient and Modern, New York, 1935.
52. Haymann, H.: Ztschr. f. d. ges. Neurol. u. Psychiat., **15**, 511, 1913.
52a. Hereford, M.: Magazine "She," **1**, 6, 1943.
53. Hermstein, A.: Arch. f. Gynäk., **130**, 80, 1927.
54. Hilgard, E. R., and Marquis, D. G.: Conditioning and Learning, New York, 1940.
55. Hirsch, G., and Hartmann, E.: Zentralbl. f. Gynäk., **50**, 2883, 1926.
56. Holler, A., Melicher, H., and Reiter, N.: Ztschr. f. klin. Med., **100**, 564, 1924.
57. Jacobi, M. P.: The Question of Rest for Women During Menstruation, New York, 1877.
58. Jacoby, I.: Monatschr. f. Geburtsh. u. Gynäk., **92**, 337, 1932.
59. Jerusalem, M.: Wien. klin. Rundschau, **16**, 881, 1902.
60. Kersh, S.: Über Veränderungen der Körpertemperaturen, Memorabilien, **2**, 65, 1882.
61. Kisch, E. H.: Prag. med. Wchnschr., **16**, 113, 1891.
62. Klaus, K.: Biochem. Ztschr., **163**, 41, 1925.
63. Kross, I.: Am. J. Obst. and Gynec., **7**, 310, 1924.
64. Labhardt, A.: Zentralbl. f. Gynäk., **48**, 2626, 1924.
65. Labhardt, A., and Hüssy, P.: Ztschr. f. Geburtsh. u. Gynäk., **84**, 715, 1922.

66. LANCZOS, A.: Arch. f. exp. Path. u. Pharmakol., **155**, 117, 1930.

67. LAPINSKI, L.: Ann. d. sci. psychiques, Paris, **7**, 265, 1897.

68. LEVINSON, S. A.: J. Immunol., **9**, 463, 1924.

69. LEVITICUS, XV, 19-27.

70. MACCOLL, D., and SHORE, L.: Ber. u. d. ges. Physiol. u. exp. Pharmakol., **63**, 372, 1932.

71. MACHT, D. I.: Am. J. Med. Sci., **140**, 839, 1910; (a) Med. Rec., Feb. 26, 1910; (b) Charlotte Med. J., **66**, 160, 1912; (c) J. Am. Med. Assn., **68**, 1230, 1917; (d) J. Urol., **2**, 43 and 211, 1918; (e) J. Pharmacol. and Exp. Ther., **10**, 509, 1918; (f) Bull. Johns Hopkins Hosp., **30**, 38, 1919; (g) J. Pharmacol. and Exp. Ther., **22**, 123, 1923; (h) J. Pharmacol. and Exp. Ther., **24**, 213, 1924; (i) J. Pharmacol. and Exp. Ther., **29**, 461, 1926; (j) J. Am. Med. Assn., **89**, 753, 1927; (k) Am. J. Obst. and Gynec., **16**, 263, 1928; (l) J. Urol., **20**, 733, 1928; (m) J. Philippine Islands Med. Assn., p. 523, 1925; (n) Science, **71**, 302, 1930; (o) Proc. Soc. Exp. Biol. and Med., **32**, 349, 1934; (p) Fol. ophthal. orient., **1**, 358, 1935; (q) J. Am. Med. Assn., **110**, 409, 1938; (r) Arch. internat. de pharmacodyn. et de ther., **58**, 221, 1938.

72. MACHT, D. I., and ANDERSON, W. T.: J. Pharm. and Exp. Ther., **34**, 365, 1925.

73. MACHT, D. I., and BLOOM, W.: Arch. internat. de pharmacodyn. et de ther., **25**, 379, 1920.

74. MACHT, D. I., and BROOKS, D. J.: Am. J. Physiol., **133**, 371, 1941.

75. MACHT, D. I., and DAVIS, M. E.: J. Comp. Psychol., **18**, 113, 1934.

76. MACHT, D. I., and ELVERS, C. F.: Proc. Soc. Exp. Biol. and Med., **21**, 254, 1924.

77. MACHT, D. I., and GARDNER, R. E.: Proc. Nat. Acad. Sc., **22**, 384, 1936.

78. MACHT, D. I., and GRUMBEIN, M. L.: Arch. internat. de pharmacodyn. et de ther., **60**, 95, 1938.

79. MACHT, D. I., and HANDMAN, O. R.: (a) Proc. Soc. Exp. Biol. and Med., **22**, 208, 1925; (b) J. Pharm. and Exp. Ther., **22**, 483, 1924.

80. MACHT, D. I., and LEACH, H. P.: Bull. Johns Hopkins Hosp., **46**, 225, 1930.

81. MACHT, D. I., and LIVINGSTON, M. B.: J. Gen. Physiol., **4**, 573, 1922.

82. MACHT, D. I., and LUBIN, D. S.: (a) Proc. Soc. Exp. Biol. and Med., **20**, 265, 1923; (b) J. Pharmacol. and Exp. Ther., **22**, 413, 1924.

83. MACHT, D. I., and MACHT, M. B.: J. Lab. and Clin. Med., **26**, 597, 1941.

84. MACHT, D. I., MACHT, M. B., and BURTSICK, L. L.: Am. J. Physiol., **133**, 372, 1941.

85. MACHT, D. I., and MORA, C. F.: J. Pharm. and Exp. Ther., **16**, 216, 1920.

86. MACHT, D. I., and PELS, I. R.: Proc. Soc. Exp. Biol. and Med., **25**, 237, 1927.

87. MACHT, D. I., and SEAGO, D. W.: J. Comp. Psychol., **4**, 151, 1924.

88. MACHT, D. I., and ULRICH, J. L.: J. Urol., **8**, 99, 1922.

89. MACKENZIE, —.: J. Ment. Sc. (London), **54**, 116, 1908.

90. MANDELSHTAM, A., TSCHAIKOWSKY, W., and BONDARENKO, G.: Arch. f. Gynäk., **154**, 636, 1933.

91. MAYHER, E.: Monatschr. f. Kinderh., **38**, 98, 1928.

92. MEIROWSKY, E.: Deutsch. med. Wchnschr., **36**, 1444, 1910.

93. MERLETTI, C.: La Funzione mestruale, Ann. di ostetr. e ginecol., **22**, 673, 1900.

94. MICHIN, B. W.: Abstr., Zentralbl. f. Gynäk., **27**, 1390, 1903.

95. MOMMSEN, H.: Monatschr. f. Kinderh., **62**, 93, 1934.

96. MONTAGU, M. F. A.: Quart. Rev. Biol., **15**, 211, 1940.

97. MOORE, L. M., and JENKINS, L. M.: Proc. Soc. Exp. Biol. and Med., **29**, 297, 1931.

98. NAPIER, L.: Brit. Gynec. J., **12**, 176, 1896.

99. NOVAK, E.: (a) Menstruation and Its Disorders, New York, 1931; (b) Gynecology and Female Endocrinology, Boston, 1941.

100. OKEY, R., and BOYDEN, R. E.: J. Biol. Chem., **72**, 261, 1927.

101. OPEL, P.: Über Menstrualexantheme, Leipzig, 1908.

102. OSLER, W., and McCRAE, T.: System of Medicine, 9th ed., 1920.

103. PELS, I. R., and MACHT, D. I.: (a) Arch. Dermat. and Syph., **19**, 640, 1929; (b) Arch. Dermat. and Syph., **23**, 601, 1931.

104. PLINY, the Elder: Natural History (60 A.D.); trans. by Bostock and Riley, 1855, Book 7, Ch. 13, Book 28, Ch. 23.

105. PLÖNIES, W.: Arch. f. Verdauungskr., **14**, 670, 1908.

106. POLANO, O., and DIETL, K.: München. med. Wchnschr., **71**, 1385, 1924.

107. Queries and Minor Notes: J. Am. Med. Assn., **120**, 326, 1942.

107a. Ibid: J. Am. Med. Ass., **122**, 981, 1943.

108. RABUTEAU, C.: Gaz. de Paris, Nr. 51.

109. RAHN, O.: Invisible Radiation of Organisms, Berlin, 1936.

110. RAHN, O., and BARNES, M. N.: J. Bacteriol., **25**, 28, 1933.

111. REINL, C.: Die Wellenbewegung der Lebensprozesse des Weibes, Volkmann's Samml. klin. Vorträge, Nr. 243, 1884.

112. ROSENSTRAUS, S.:   Menstruation und innere Krankheiten, Berlin, 1912.
113. ROSS, J. F. W.:   J. Ment. Sci., 55, 270, 1909.
114. RUBENSTEIN, B. B.:   Endocrinology, 22, 41, 1938.
115. RUGH, J. T.:   Am. J. Surg., 25, 126, 1934.
116. SÄNGER, H.:   Zentralbl. f. Gynäk., 45, 819, 1921.
117. SENATOR, H.:   Berl. klin. Wchnschr., 9, 615, 1872.
118. SCHÄFFER, R.:   Veit's Handbuch d. Gynäk., 3, 4, 1908.
119. SCHERINGER, W.:   Arch. f. Gynäk., 145, 172, 1931.
120. SCHICK, B.:   Wien. klin. Wchnschr., 19, 1, 1920.
121. SCHRÄDER, T.:   Ztschr. f. klin. Med., 25, 72, 1894.
122. SHAPIRO, B.:   Purity of Family Life (Heb.), Kaunas, 1936.
123. SIEBURG, E., and PATZSCHKE, W.:   Ztschr. f. d. ges. exp. Med., 36, 324, 1923.
124. SILBER, W.:   Ztschr. f. Kinderh., 49, 210, 1920.
125. SIREDEY, A.:   Wien. klin. Wchnschr., p. 553, 1905.
126. SMITH, O. W., and SMITH, G. S.:   Proc. Soc. Exp. Biol. and Med., 44, 100, 1940.
127. SPIEGLER, R.:   Arch. f. Gynäk., 134, 322, 1928.
128. STEINERT, J., and PAPP, G.:   Ztschr. f. Kinderh., 56, 208, 1934.
129. SUTTERLIN, T., and SZELINSKI, D.:   Ber. u. d. ges. Physiol. u. exp. Pharmakol., 63, 436, 1932.
130. SWANBERG, T. H.:   J. Nerv. and Ment. Dis., 50, 224, 1919.
131. TEDSTROM, M. K., and WILSON, L. E.:   Calif. and West Med., 44, 375, 1936.
132. THOMA, E.:   Allg. Ztschr. f. Psychiat., 2, 590, 1894.
133. TÖBLER, M.:   Monatschr. f. Geburtsh. u. Gynäk., 22, 1, 1905.
134. TRUESDELL, D., and CROXFORD, G.:   Am. J. Physiol., 79, 112, 1926.
135. TUTTLE, W. W.:   J. Lab. and Clin. Med., 11, 60, 1925.
136. UNNA, P. G., and GOLODETZ, I.:   Biochem. Ztschr., 20, 469, 1909.
137. VER EECKE: Bull. de l'Acad. roy. de méd. belg., Bruxelles, 1897.
138. VON OTT, D.:   Zentralbl. f. Gynäk., 14, 31, 1890.
139. WAKEHAM, G.:   J. Biol. Chem., 56, 55, 1923.
140. WALDBOTT, G. L., and BAILEY, L. J.:   J. Allergy, 13, 125, 1942.
141. WALLIN, C. C.:   J. Am. Med. Assn., 51, 2157, 1908.
142. WIBLE, C. L.:   J. Lab. and Clin. Med., 17, 14, 1931.
143. WIESSNER: Zentralbl. f. Gynäk., 23, 1335, 1899.
144. WILLIAMS, L.:   Clin. J. London, 33, 325, 1908-9.
145. WOODWORTH, R. S.:   Experimental Psychology, New York, 1938.
146. WORONYTSCH, N.:   Wien. klin. Wchnschr., 27, 937, 1914.
147. ZONDEK, B.:   Hormone des Ovariums und des Hypophysenvorderlappens, 2d ed., Berlin, 1935.

ACUTE INFECTIOUS POLYNEURITIS (GUILLAIN-BARRÉ SYNDROME)

A BRIEF REVIEW OF THE LITERATURE WITH REPORT OF 3 CASES

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SINCE the publication by Guillain-Barré and Strohl[13] of a group of cases exhibiting a form of acute polyneuritis (or radiculoneuritis, as Barré called it), a good number of such reports of this disease in children have been published.[1,4–8,11,15,18,19]   Casamajor and Alpert[4] collected the data on 19 cases in children, and added data on 3 children who had been studied by them. Since this latter report, De Sanctis and Green[8] have reported 2 additional cases, and in the excellent paper on this

disease by Roseman and Aring,[9] data on 4 children are included in a thorough study of 16 cases.

We have observed 3 children during a few months whose signs, symptoms and spinal fluid studies were such that we are reporting them as representing the picture described in the literature as Guillain-Barré syndrome (Tables 1 and 2).

TABLE 1. SUMMARY OF DATA IN THREE CASES OF GUILLAIN-BARRÉ'S SYNDROME.

Age (yrs.) Sex	Preceding illness	Initial symptoms	Findings in hospital	Course and comment
7-M	Cold 7 days, ... sore throat ..., irritable	Weakness of legs noted 2 days before adm.; couldn't stand 1 day of adm.	Decreased power in arms, hands, thighs, feet, with hyperemia, deep reflexes absent in arms, very sl. in legs; cranial nerves intact, mod. nuchal rigidity; gen. muscular tenderness in arms and legs	Much impr. in 2 wks. after adm.; entirely recovered after 41 days; T.P.R. normal throughout hospital stay
2-F	Malaise 1 wk. ..., vomiting 1 day; intermittent headache 3 days; loss of appetite 1 wk.	Wilhel had a muscle weakness noted, during first 4 days after a lm., progressive weakness of legs, esp. of thighs	3 days after adm., lethargy, no nuchal rigidity, b-lat. periph. facial palsy, marked weakness of all muscles of legs, esp. thigh; complained of pain and tenderness in thigh and neck muscles	Impr. began 8 days after adm., but w. no nuchal rigidity for 4 wks. after adm.; able to walk 6 wks. after adm. and on discharge (2) mos. after adm.) had regained most of her muscle power; no definite muscle atrophy; areflexia in legs still present
8-M	No preceding illness recorded; vomited twice 4 days ago	Pain and stiffness in knees for 4 days	Mod. nuchal rigidity; weakness of leg muscles, esp. thigh; triceps, biceps reflex decr.; knee jerk, ankle jerk ab.; cranial nerves intact; severe pain in thigh and back muscles	Impr. rapidly, but complained of vague pains in shoulder, arms, legs occ. for 2 wks. after adm.; 31 days after adm. pt. had no complaints, was getting strong and able to walk; discharged 43 days after adm. with only a slight limp remaining

TABLE 2.—RESULTS OF EXAMINATION OF THE SPINAL FLUID

Date 1942	Cells	Protein (mg. per 100 cc.)
CASE 1		
1-15	2	51
1-19	6	112
1-22	1	115
1-30	2	qns
2- 6		67
2-24	2	46
CASE 2		
3-24	1	100
3-27	0	100
3-30	0	71
4-20	0	170
5- 6	...	qns
5-13		78
5-28	..	46
CASE 3		
4-28	0	60
4-29	0	qns
5- 6		
5- 8	0	126
5-21	6	340
5-28	1	qns
7- 8	3	76

Discussion. These 3 cases had symptoms, physical findings and spinal fluid changes that probably justify their being classified as cases of Guillain-Barré's syndrome, known by many synonyms.*

The disease occurs most often in winter and spring. It shows no predilection for either sex, and apparently afflicts nearly all age groups, although none of the reported cases have been in children under 2 years of age. In the group of 19 cases collected from the French literature by Casamajor and Alpert[4] there were 9 cases under the age of 5 years, with 4 being 2 years old. So far, no etiologic agent has been proven as the cause of the disease.

In practically all of the reported cases the onset of the disease has been preceded by an upper respiratory infection. This latter infection in some cases preceded the disease by a week or more, and in others by a few days, or was present when paralysis occurred. Aches and pains are generally present, and these may be severe; tingling and burning may be annoying at times, while muscle tenderness is often marked. These sensory disturbances last for a varying length of time. One of our patients complained of pain on flexion of the neck for nearly a month; on the other hand, the sensory symptoms may last only a few hours, and occasionally the motor symptoms do not appear for days.

The weakness usually appears first in the distal muscles of the lower extremities, with a symmetrical involvement, which is valuable in diagnosis. Often within hours there is rapid involvement of muscle groups of the arms, with facial paralysis; and occasionally bladder and rectal sphincter loss. Cord involvement seems to be definitely less frequent in children than adults. This is true, also, of bulbar symptoms.

The changes in reflexes seem to be a rather constant finding, with all tendon reflexes in the involved limb absent, or diminished. Although facial paralysis is reported as being common, many of the children reported do not show it. From the total of 19 cases collected by Casamajor and Alpert,[4] and the 3 cases added by them, only 7 had facial paralysis, with another case being questionable. One of our cases had definite facial paralysis, and weakness of the right side of the tongue. Among the 16 cases studied by Roseman and Aring[19] there were 4 children, and 3 of these showed facial palsy. The paralysis when present is of the nuclear or infranuclear type, with involvement of the lower part of the jaw, brow and eyelid. Other cranial nerves than the seventh may be involved, but their involvement has not been reported as often in children as in adults.

There is mild systemic reaction as judged by the temperature and pulse rate. Most patients have either a slight fever or a normal temperature, with a normal, or only slightly increased leukocyte count. But the spinal fluid change is one of the most interesting and characteristic features of this disease. The typical spinal fluid finding is a normal cell count with a definitely increased protein content. Guillain-Barré

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* Acute polyneuritis, infectious polyneuritis, motoneuritis, acute polyneuritis with facial diplegia, acute ascending paralysis.

and Strohl[13] in their original article stressed this finding, and Guillain[16] more recently has again emphasized the importance of albuminocytologic dissociation of cell count and albumin in the spinal fluid in the diagnosis of infectious polyneuritis. However, there are some practical points in this connection. The high protein content of the spinal fluid may not appear for a week or two after the patient becomes ill. Repeated taps may be required to find the change; but in some cases it may persist for years. It may be moderately increased or quite high, say, between 100 and 800 mg. per 100 cc. Unless the clinical picture is most typical, it would seem unwise to classify a disease as belonging to the one under discussion without a definitely increased spinal fluid protein, in the presence of a normal cell count. Quite a good number of the cases studied by Roseman and Aring and of those collected by Casamajor and Alpert had inconclusive spinal fluid studies. Repeated taps should be made as indicted. As has been emphasized,[4] similarity of this disease to acute poliomyelitis makes a diagnosis in the very early stage most difficult and important, and the spinal fluid picture is very helpful.

The pathologic picture has been studied by Holmes,[16] Bradford, Bashford, and Wilson,[2] Casamajor,[3] Viets,[21] Greenfield and Carmichael,[12] Sabin and Aring,[20] Honeyman,[17] and Roseman and Aring.[19] The report of the latter two writers is especially thorough and detailed. Microscopically, they report a moderate degree of edema of brain, spinal cord, and peripheral nerves. Acute passive congestion and toxic changes in the liver, kidneys, heart, and spleen; there was varying degrees of atelectasis of the lower lobes of the lungs, and an acute bronchitis. Microscopic studies of the nerves showed marked edema of the bundles, congestion, infiltration of inflammatory cells, swelling and beading of myelin sheaths, and fragmentation, beading and swelling of axis cylinders. The cord revealed some involvement of the cells of the gray columns in all cases, with the changes being most conspicuous at the cervical and thoracic level. Vacuoles were found in the cytoplasm of some of the anterior horn cells. Irregularity in the size of the axones was noted in the white matter of the cord.

The brain stem changes were rather similar to those of the spinal cord, while the cerebral hemisphere and cerebellum showed "outfall" of nerve cells, shrinkage of the ganglion cells, congestion, swelling of the oligodendroglia of the white matter and cellular infiltration of the meninges. Microscopically, studies of the viscera showed areas of degeneration in the adrenal cortex, interstitial infiltration of the heart, focal necrosis of liver cells with areas of focal degeneration; the kidneys showed collections of mononuclear cells, while in the spleen there was an extreme abundance of red cells.

The prognosis as to life is good in this disease, as it is seen in children, although the mortality is rather high among adults. In a series of 26 cases, of which 3 were children, reported by Forster, Brown and Merritt,[10] the mortality rate was 42%. Of the 3 children in their group, 2 died. However, of the 22 cases in Casamajor's and Alpert's report there was only 1 death. Both of De Sanctis' and Green's cases, the 4 children in Roseman's and Aring's series, and our 3 cases recovered.

The prognosis as to complete recovery of muscle function is more difficult to determine from the reported cases. In many instances the patients were not followed for a long period of time, or information is so recorded that one cannot be sure of the exact state of muscle function. "Gradual improvement" is often the final note made; or a patient may be described as being "well" when last seen. Of the 22 cases in Casamajor's and Alpert's report, there were 13 in which recovery seemed complete. It would seem, that while there is a good outlook for a return of normal muscle function, the improvement may take many months. The rapidity with which improvement begins seems to indicate a good prognosis. The chief ill-effects that are seen usually consist of weakness of the involved muscles with contractures.

Summary. Three cases are reported whose signs and symptoms and spinal fluid findings were such that they have been classified as belonging to the Guillain-Barré syndrome.

A brief discussion of the clinical picture has been presented.

REFERENCES

1. Bassoe, P.: Arch. Path., **26**, 289, 1938.
2. Bradford, J. R., Bashford, E. F., and Wilson, J. A.: Quart. J. Med., **12**, 88, 1918.
3. Casamajor, L.: Arch. Neurol. and Psychiat., **2**, 605, 1919.
4. Casamajor, L., and Albert, G. R.: Am. J. Dis. Child., **61**, 99, 1941.
5. Clement, M., and Ketelbant: J. belge de neurol. et de psychiat., **38**, 240, 1938.
6. Cohen, J.: J. belge de neurol. et de psychiat., **38**, 307, 1938.
7. Dagnelie, J.: J. belge de neurol. et de psychiat., **38**, 282, 1938.
8. DeSanctis, A. G., and Green, M.: J. Am. Med. Assn., **118**, 1445, 1942.
9. Ford, F.: Diseases of Nervous System in Infancy, Childhood and Adolescence, Springfield, Ill., Charles C Thomas, p. 553, 1927.
10. Forster, F. M., Brown, M., and Merritt, H. H.: New England J. Med., **37**, 225, 1941.
11. Gilpin, S. F., Moersch, F. P., and Kernohan, J. W.: Arch. Neurol. and Psychiat., **35**, 937, 1936.
12. Greenfield, J. G., and Carmichael, E. A.: Brain, **58**, 483, 1935.
13. Guillain, C., Barré, J. A., and Strohl, A.: Bull. et mém. Soc. méd. d. hôp. de Paris, **40**, 1462, 1916.
14. Guillain, G.: Arch. Neurol. and Psychiat., **36**, 975, 1936.
15. Hecht, M. S.: J. Pediat., **11**, 743, 1937.
16. Holmes, G.: Brit. Med. J., **2**, 37, 1917.
17. Honeyman, W. M.: Bull. Neurol. Inst. New York, **6**, 519, 1937.
18. Mettel, H. B.: J. Michigan Med. Soc., **23**, 47, 1924.
19. Roseman, E., and Aring, C. D.: Medicine, **20**, 463, 1941.
20. Sabin, A. B., and Aring, C. D.: Am. J. Path., **17**, 469, 1941.
21. Viets, H. R.: Arch. Neurol. and Psychiat., **17**, 794, 1927.

HYPERGLOBULINEMIA

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ALMOST invariably when the total protein concentration of blood serum is increased above normal this increase is because of an increase in serum globulin concentration.[15] A study of hyperproteinemia is,

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therefore, essentially a study of hyperglobulinemia. Furthermore, with three major exceptions,* whenever the globulin concentration is increased above normal the total protein concentration is usually also increased above normal.[15]

In 1937 Jeghers and Selesnick[10] reviewed the subject of hyperproteinemia and presented 13 cases due to 6 different causes. In this paper we shall present 50 cases due to 16 different causes. These 50 cases represent 9% of a series of 576 patients on whom 995 determinations of blood serum protein were done. The data were collected over a period of 3 years. The analyses were done by a macro-Kjeldahl modification of the Howe* procedure and the author's falling drop technic.[15]

Hyperglobulinemia is considered to exist when the serum globulin concentration is above 3 gm. per 100 cc. or when, in the absence of a globulin determination, the total protein concentration is above 8 gm.[14,15] Whenever the total protein concentration is above 7.5 gm., an abnormal increase in serum globulin is suspected but is considered to be certain only upon actual determination of the globulin concentration.

Of the total number of cases studied, 35 (6.1%) were found to have values for total protein concentration above 8 gm. Values between 7.5 and 8 gm. were found in only 20 patients out of the total of 576. Because in our study of 150 normal individuals[14] we found only 1 with a total protein concentration above 7.5 gm. (7.6 gm.), these 20 were considered as suspicious. However, only the 15 in which the serum globulin concentration was shown to be above normal were included in our statistical analysis. These 15 cases plus the 35 noted above comprise all the cases of hyperglobulinemia discussed below and constitute 9% of the total number of cases studied.

Bing and Plum[2] have presented clinical evidence which suggests that the origin of globulin is in the plasma cell of the bone marrow and in the reticulo-endothelial cells everywhere. Sabin[24] has reviewed immunologic and cytologic evidence which supports this theory. There also seems to be some relationship between globulin formation and the liver. An increase in serum globulin occurs in hepatic involvement of various kinds and is particularly common and marked in cirrhosis.[16] Aside from its rôle as antibody almost nothing is known of the functions of globulin. The evidence showing that the circulating antibodies are contained in the globulin fraction of serum has been recently reviewed.[23]

Diseases Involving Bone Marrow. The accompanying table shows the results obtained in diseases involving the bone marrow. The highest value for serum protein concentration obtained in this entire study was 10.1 gm.; this was in a case of monocytic leukemia which

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* These three major exceptions are: (1) all forms of hepatic disease; (2) acute glomerulonephritis; and (3) the simultaneous occurrence of two conditions, the one causing hyperglobulinemia, the other causing hypoalbuminemia. These conditions have been discussed in an earlier report and will not be considered here.[15] In these instances the globulin concentration is frequently increased but the albumin concentration is at the same time frequently decreased so that the total protein concentration does not always increase when the globulin is increased.

was proven by autopsy. The patient had a serum globulin concentration varying between 4.3 and 6.7 gm. This case is of considerable interest because the monocyte is generally considered to be part of the reticulo-endothelial system. Should such marked increases of serum globulin be found to be usual in this disease, it would lend further support to the theory that globulin is formed by the reticulo-endothelial system.

In our 1 case of lymphatic leukemia there was an increase in serum globulin. There are reports in the literature of increased serum globulin in 2 cases of myeloid[7,12] and 1 of lymphatic leukemia,[11] but the incidence is not known. In neither lymphatic nor myeloid leukemia, however, are the increases nearly as striking as in the case of monocytic leukemia cited above.

The association of hyperproteinemia with multiple myeloma was probably first shown in 1917 by Jacobsen.[9] The highest serum protein concentrations reported in the literature have been in this disease and were 23.4 gm. by Schumacher, Williams, and Coltrin,[25] and 18.4 gm. by Foord and Randall.[6] Of the 13 cases of hyperproteinemia reported from the Boston City Hospital,[10] 7 had multiple myeloma. Although in the present study there were only 2 cases of this disease, neither of which showed hyperproteinemia, the author has since learned directly of 4 cases which were detected because of the hyperproteinemia found in their blood, analyzed for other reasons. From a review of the literature, Jeghers and Selesnick concluded that 50% to 60% of the cases of multiple myeloma have hyperproteinemia and that the serum protein determination is a more valuable aid in its diagnosis than the search for Bence-Jones protein in the urine. Ulrich[29] stated that hyperproteinemia is frequently present in the absence of Bence-Jones protein in the urine and *vice versa*. Since the tumor cell of multiple myeloma is the plasma cell, and since the concentration of serum globulin is so markedly and frequently increased in this disease, this suggests that the plasma cell is a source of formation of serum globulin. The plasma cell is considered by some to be a part of the reticulo-endothelial system.

Peters and Eisenman[22] found that metastasis to the bone marrow from primary carcinoma elsewhere may be associated with hyperproteinemia. Such cases usually have metastases to the liver as well. Metastases of carcinoma to the liver are frequently associated with hyperglobulinemia.[16] It is difficult, therefore, with the evidence at hand to determine whether the metastasis to the liver or that to the bone marrow is responsible for the hyperglobulinemia in these cases.

Chronic Infections. Of the 50 cases of hyperglobulinemia studied in this series, 31 were due to infection (Table 1). These infections were all chronic, either suppurative or non-suppurative. None was acute.

In 30 cases of acute infection, both suppurative and non-suppurative (not included in this table), such as pneumonia, mastoiditis, tonsillitis, cervical adenitis, etc., there was no increase in total serum protein above normal and only 2 showed slight increase in serum globulin.

The exact nature of the globulin increase in the chronic infections

is not known. If the entire increase of serum globulin were due to active antibodies, one might logically expect that the body would thereby be protected against such prolonged and serious infections. Perhaps much of this serum globulin is not active antibody but is rather the result of antibody antigen interaction.[23] Perhaps the increase is a compensatory mechanism for the absence of some missing factor such as complement.

TABLE 1. SUMMARY OF DATA ON HYPERPROTEINEMIA AND HYPERGLOBULINEMIA

	Total protein				Globulin	
	No. cases	No. deter.	No. cases >7.5 gm per 100 cc.	No. deter. >7.5 gm per 100 cc.	No. deter.	No. deter. >3 gm per 100 cc.
Dehydration						
Various causes	22	28	17	17	20	15
Diseases involving bone marrow						
Monocytic leukemia	1	4	1	1	1	4
Multiple myeloma	2	1	0	0	1	1
Lymphatic leukemia	1	1	1	1	1	1
Infections:						
Abscess of lung	1	6	1	5	2	2
Bronchiectasis	5	7	1	1	1	1
Chronic pyonephrosis	1	4	1	1	2	2
Chronic osteomyelitis	1	1	0	0	1	1
Boeck's sarcoid	1	1	0	0	1	1
Tuberculosis	12	29	3	4	20	16
Syphilis	12	15	6	6	5	3
Venereal lymphogranuloma	11	11	8	10	8	7
Rheumatoid arthritis	1	1	1	1	1	1
Bacterial endocarditis	7	14	2	6	3	2
Lupus erythematosis disseminatus	2	3	2	2	2	2
Periarteritis nodosa	2	4	0	0	4	4

Of the 9 cases of pulmonary non-tuberculous suppuration (lung abscess and bronchiectasis) all but 1 had total protein concentrations above 7.5 gm. at some time in their course. The highest values seen in any of the infections were in patients with pulmonary abscess. These cases like those having chronic pyonephrosis and chronic osteomyelitis may be considered in a group of chronic suppurative infections in which hyperproteinemia is apparently common.

Hyperglobulinemia was also found in the chronic non-suppurative infections: tuberculosis, Boeck's sarcoid, syphilis, venereal lymphogranuloma, rheumatoid arthritis, bacterial endocarditis, lupus erythematosis disseminata, and periarteritis nodosa. The literature indicates that leprosy and kala-azar should also be added to this group.

In tuberculosis, Boeck's sarcoid, syphilis, venereal lymphogranuloma, leprosy, and kala-azar the mononuclear cell and macrophage are a prominent part of the pathologic picture. Furthermore, the bone marrow in the latter 5 diseases is said to resemble that in multiple myeloma because of the accumulation of plasma cells. The presence of hyperglobulinemia in these conditions emphasizes again, therefore, the relationship between the reticulo-endothelial system and globulin formation.

In an article by Eichelberger and McCluskey[5] there are tables showing results of 150 determinations of plasma proteins on their

109 patients with tuberculosis. Study of these tables reveals that the total protein concentration was above 8 gm. in 44% of the determinations, the globulin concentration above 3 gm. in 62% and the albumin below 4 gm. in 17%. In none of their cases was the total protein concentration below normal. These changes were essentially the same as those found in 12 cases of tuberculosis studied in the present series and in 38 cases studied by Stempien and Kagan[26] at the Willard Parker Hospital. In the latter 50 cases, however, hypoalbuminemia and decreased total protein were seen with greater frequency. In tuberculosis the infection probably is responsible for the increased serum globulin concentration and malnutrition is probably responsible, for the most part, for producing the decreased albumin concentration.

Kampmeier, Smith and Larsen[18] found hyperproteinemia in 62 of the 67 cases of venereal lymphogranuloma which they studied and considered this fact to be of diagnostic value. Hyperproteinemia was present in 8 of our 11 cases.

In our only case of rheumatoid arthritis, hyperproteinemia was present. Davis[4] found this to be most marked in the severe cases and noted normal serum protein in the quiescent stages. He considered the increased globulin to be further evidence of the infectious nature of this disease. Taussig[28] found similar changes in the blood of 2 children with Still's disease.

Kürten[19] found hyperproteinemia in 33 of his 35 cases of bacterial endocarditis. It was present in 5 of the 7 cases in this series at some time in their course. Two cases of lupus erythematosis and 2 cases of periarteritis nodosa were also associated with increased globulin. The latter three generally fatal diseases have a number of other clinical similarities, and pathologically they are often considered together.

Hyperglobulinemia was seen in 50% of the determinations done in a study of patients with acute glomerulonephritis.[17] The increase in globulin in this condition is probably again due to the associated infection. It is to be noted that this is one of the three conditions mentioned above in which the serum albumin concentration is sufficiently lowered so that the total protein concentration is often normal in spite of the globulin increase.

Of the infections studied, only abscess of the lung, subacute bacterial endocarditis, and venereal lymphogranuloma were associated with total protein concentrations above 9 gm.

Dehydration. The 22 cases of dehydration were secondary to various causes such as alcoholism, diarrhea, and coma. Of the 28 determinations, 17 showed an increase in total protein. In each of these cases in which globulin was determined it was the responsible factor. In none of the cases was the albumin concentration increased, and in 4 it was below normal. Three of the latter had had chronic diarrhea, which accounted satisfactorily for the hypoalbuminemia in spite of dehydration. The 4th patient was a chronic alcoholic who had long been on a protein starvation diet.

One would expect that in dehydration serum albumin would become

concentrated just as are the other blood constituents such as globulin and hemoglobin. However, we have not found this to be the case in any of the 22 cases of dehydration studied, even though most of these showed increased globulin and hemoglobin concentrations. This finding has been borne out in other patients whom we have since studied during the progress of dehydration. Just what happens to the albumin which is lost from the blood stream during the process of dehydration is not apparent. Talbott,[25] in 1935, felt that an increase in capillary permeability during dehydration might account for loss of some of the albumin from the blood. The observation of a slight albuminuria in some patients during marked dehydration would seem to be familiar evidence to support this. One may question, however, whether the amount which is lost in this manner, even when all the capillaries throughout the body are involved, is sufficient to account for the large amount of albumin lost from the blood in some cases of dehydration. Both Kürten[20] and Bing[1] have found that when serum is heated for $\frac{1}{2}$ hour at 57° C. some of the albumin is converted to globulin. Whether or not this might occur within the body under any circumstances has not been reported. We are, therefore, faced with these questions: Is there an upper threshold of serum albumin concentration? If there is, how constant is it and by what mechanism is it maintained?* The answers to these questions are obviously of great clinical importance.

Mandelbaum,[21] in 1936, reviewed the various causes of dehydration and discussed the associated hyperproteinemia. Bridge and Cohen[3] reported on the value of serum protein concentration as a guide in the treatment of dehydration.

Shock. In this study there was no opportunity to study the increases in total protein concentration in shock which have been reported by a number of investigators.

Summary. The significance of hyperglobulinemia has been discussed from a clinical and physiologic point of view. Hyperglobulinemia appears principally in diseases involving the bone marrow, chronic infections, diseases involving the liver, and in dehydration.

The accompanying table classifies the cases studied in accordance with the above discussion. According to this study and the literature, values for total serum protein concentration over 9 gm. are rarely found except in multiple myeloma, monocytic leukemia, venereal lymphogranuloma, pulmonary suppuration, Boeck's sarcoid, subacute bacterial endocarditis, and dehydration. (A few diseases which are rare in this country, such as kala-azar and schistosomiasis, may also produce such changes.)

The presence of an upper threshold of albumin concentration in dehydration is suggested. Increase in the total protein concentration during dehydration in the cases studied was due to an increase in serum globulin while the serum albumin remained at the upper level of normal or was decreased due to other factors.

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* Experiments to help determine these points were begun, but because of the author's entering the Armed Services were not carried to completion.

The clinical data presented support the theory that serum globulin is formed by the plasma cells and the reticulo-endothelial system throughout the body.

REFERENCES

1. BING, J.: Acta med. Scandin., **91**, 336, 1937.
2. BING, J., and PLUM, P.: Acta med. Scandin., **92**, 415, 1937.
3. BRIDGE, E. M., COHEN, M. I., and SCOTT, T. F. McN.: J. Pediat., **18**, 709, 1941.
4. DAVIS, J. S., JR.: J. Lab. and Clin. Med., **21**, 478, 1936.
5. EICHELBERGER, L., and McCLUSKEY, K. L.: Arch. Int. Med., **40**, 831, 1927.
6. FOORD, A. G., and RANDALL, L.: Am. J. Clin. Path., **5**, 532, 1935.
7. GROS, W.: Deutsch. Arch. klin. Med., **177**, 461, 1935.
8. HOWE, P. E.: (a) J. Biol. Chem., **49**, 93, 1921; (b) Ibid., **49**, 109, 1921.
9. JACOBSEN, V. C.: J. Urol., **1**, 167, 1917.
10. JEGHERS, H., and SELESNICK, S.: Internat. Clin., **3**, 248, 1937.
11. JOHANSEN, A. H.: Bibl. f. Læger, **125**, 379, 1933.
12. KEILHACK, H.: Folia hæmatol., **55**, 406, 1936.
13. KAGAN, B. M.: J. Clin. Invest., **17**, 369, 1938.
14. KAGAN, B. M.: J. Lab. and Clin. Med., **27**, 1457, 1942.
15. KAGAN, B. M.: Arch. Int. Med., **71**, 157, 1943.
16. KAGAN, B. M.: (In press.)
17. KAGAN, B. M.: (In press.)
18. KAMPMEIER, R. H., SMITH, D. W., and LARSEN, R. M.: AM. J. MED. SCI., **198**, 516, 1939.
19. KÜRTEN, H.: Ztschr. f. d. ges. exper. Med., **61**, 494, 1928; Klin. Wchnschr., **8**, 1704, 1929; cited by Jeghers, H., and Selesnick, S. (Ref. 10), p. 257.
20. KÜRTEN, H.: Biochem. Ztschr., **135**, 536, 1923; cited by Bing, J. (Ref. 1), p. 340.
21. MANDELBAUM, H.: Internat. Clin., **2**, 116, 1936.
22. PETERS, J. P., and EISENMAN, A. J.: Am. J. MED. SCI., **186**, 808, 1933.
23. SABIN, F. R.: J. Exp. Med., **70**, 67, 1939.
24. SABIN, F. R.: Pub. No. 13 Am. Assn. Advanc. Sci., p. 16.
25. SCHUMACHER, I. C., WILLIAMS, O. O., and COLTRIN, G. S.: Calif. and West. Med., **47**, 174, 1937.
26. STEMPIEN, S., and KAGAN, B. M.: (Unpublished.)
27. TALBOTT, J. H.: Medicine, **14**, 323, 1935.
28. TAUSSIG, A. E.: J. Lab. and Clin. Med., **23**, 833, 1938.
29. ULRICH, H.: Arch. Int. Med., **64**, 994, 1939.

CALCIUM SALTS OF SULFADIAZINE AND SULFATHIAZOLE: WITH PARTICULAR REFERENCE TO THEIR SUBCUTANEOUS ADMINISTRATION*

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SINCE the original report of Taplin and his associates[18] concerning the administration of sodium sulfapyridine by hypodermoclysis, the sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine have been used extensively in this manner at the University of Minnesota Hospi-

tals. For subcutaneous infusions, concentrations varying from 0.3%
to 1% in sterile physiologic sodium chloride solution are used. No
tissue irritation has resulted from this procedure. It was observed
that if aqueous solutions of sodium sulfapyridine were used in con-
centrations exceeding 1%, an inflammatory reaction, and sometimes
necrosis, might be provoked. Similar results followed the use of
aqueous solutions of sodium sulfathiazole, particularly when concen-
trations of 3% to 5% were employed. Because of these observations,
we have been reluctant to utilize solutions of sodium sulfadiazine for
subcutaneous infusions in concentrations above 1%.

The administration by hypodermoclysis of solutions of the sodium
sulfonamide compounds is advantageous in the treatment of certain
groups of patients. On the medical services, patients having severe
infections are frequently encountered who are unable to ingest the
sulfonamides because of coma, delirium or vomiting. In these instances
patients are given the elected sodium compound intravenously to
attain adequate blood concentrations, and then the levels are main-
tained by subcutaneous infusion until the individuals are able to toler-
ate the drug by mouth. This procedure is also followed on the surgical
services in the treatment of patients with postoperative infections.
A further advantage of such a therapeutic approach is that the fluid
and electrolyte balance is sustained. At times, it becomes increasingly
difficult to give repeated intravenous injections of the sodium sulfona-
mide compounds to small children, and the subcutaneous route has
been used successfully.

During recent months, sulfadiazine has been used extensively at
the University Hospitals and elsewhere, particularly for the treatment
of streptococcal and pneumonococcal infections. A number of reports
have appeared in the literature, discussing the absorption, excretion,
diffusion, toxicity and therapeutic effectiveness of sulfadiazine and its
sodium salt in man.   [1,4-8,13-16,19,20]   Ordinarily, sodium sulfadiazine is
given intravenously as a 5% solution in distilled water. A 5% con-
centration of sodium sulfadiazine is strongly alkaline, having a pH
value around 9.5 which would appear to preclude its use by the sub-
cutaneous route. For subcutaneous administration, the drug is usually
given in 0.3% to 1% solutions in physiologic saline. Jorgenson and
Greeley[11] have given to infants and children a 5% aqueous solution of
sodium sulfadiazine by the subcutaneous route, and report that no
tissue irritation followed such a procedure. The experimental studies
of Fox[9] would indicate that sodium sulfadiazine is less irritating to
the tissues of animals than the other commonly used sodium sulfona-
mide salts. More recently, we have treated a few adult patients with
aqueous solutions of sodium sulfadiazine given subcutaneously in con-
centrations varying from 1% to 5%. Local tissue irritation and ten-
derness was observed with concentrations of 3% to 5%. Until more
favorable evidence is available, the routine use of sodium sulfadiazine
for subcutaneous infusions shall not exceed a concentration of 2%.
The possibility of using a sulfadiazine preparation which would permit a
more concentrated solution for subcutaneous administration prompted

us to evaluate a calcium salt of sulfadiazine, and also of calcium sulfathiazole.*

Materials and Methods. Calcium sulfadiazine is a white, crystalline, odorless and slightly bitter compound. It is less soluble than sodium sulfadiazine, having a solubility of about 5.1% in distilled water at 25° C. The compound tends to precipitate out in this concentration when physiologic saline solution is used. Calcium sulfadiazine solutions are less alkaline than the sodium salt. The pH values for different concentrations of this compound in aqueous solution as determined with the glass electrode are as follows:

5% calcium sulfadiazine in distilled water—pH 8.5
4%   "   "   "   "   "   —pH 8.4
3%   "   "   "   "   "   —pH 8.4
2%   "   "   "   "   "   —pH 8.3
1%   "   "   "   "   "   —pH 8.1

Calcium sulfadiazine was administered parenterally to a total of 24 adult patients. These men, convalescing from mild illnesses of various sorts, ranged in weight from 56 to 83 kg. All had normal renal and cardiac function. They were maintained on a general diet with a fluid intake of 2000 to 2500 cc. daily. For the injections, 4% solutions of calcium sulfadiazine in sterile distilled water were used. The pH of these solutions was 8.4. An initial dose of 4 gm. of drug was given. In 5 subjects the first injection was given subcutaneously while in 5 others the "loading" dose was administered intravenously. In all instances the first dose was followed at 12 hour intervals by two additional subcutaneous doses of 3 gm. each. Approximately 10 minutes were taken for the subcutaneous injections and 20 minutes for the intravenous injections. No generalized reactions resulted from the administration of the drug by these methods. Local reactions, except for slight tenderness which occasionally occurred at the site of subcutaneous injection, were also notably absent. Blood samples for the determination of drug levels were taken at frequent intervals for at least 36 hours. Quantitative determinations of the drug in the blood were made by the method of Bratton and Marshall.[2]†

The value of the subcutaneous administration of calcium sulfadiazine in establishing and maintaining effective drug levels in the blood was then observed in 14 patients suffering from a variety of infections. The majority of these patients had pneumonia. In each instance, the patient received an initial dose of 4 gm. of calcium sulfadiazine in a 4% aqueous solution subcutaneously. This was followed by two more subcutaneous doses of 3 gm. each in a 4% aqueous solution, given at 12 hour intervals. Thereafter, each patient received sulfadiazine by mouth in doses of 1 gm. every 4 or 6 hours, as needed, to maintain a total drug level of more than 7 mg. per 100 cc. of blood.

Blood Levels Following the Parenteral Administration of Calcium Sulfadiazine. The levels of free sulfadiazine in the blood after the subcutaneous administration of 4 gm. of calcium sulfadiazine, followed by two subcutaneous injections of 3 gm. each at 12 hour intervals, are shown in Figure 1. Maximum blood levels were usually obtained 4 or 5 hours after the subcutaneous injections. Relatively high blood levels were maintained for a period of approximately 10 hours after each dose. These blood concentrations compare favorably with those observed by other investigators after the oral administration of sulfadiazine itself or the subcutaneous injection of its sodium salt.[13–15,20] In our series,

the rate of excretion of the drug, as measured by its disappearance from the blood, did not differ significantly from that reported by the above authors. When the drug was withdrawn, the blood level of total drug fell to less than 2 mg. per 100 cc. by the end of 48 hours after the last injection.

The sulfadiazine levels in the blood after an initial intravenous dose of 4 gm. of calcium sulfadiazine, followed by two subcutaneous injections of 3 gm. each at intervals of 12 hours, are shown in Figure 2. Immediately after intravenous administration, the drug concentration in the blood was high although the actual drug levels varied considerably in different subjects. Subsequently there was a steady decline of
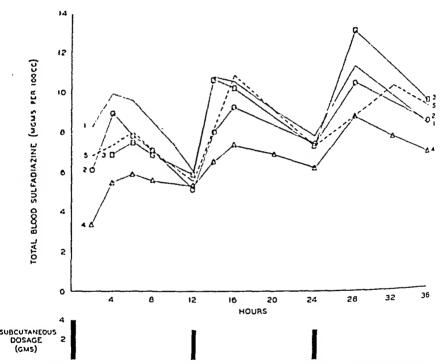
FIG. 1.—Concentrations of free sulfadiazine in the blood following repeated subcutaneous injections of calcium sulfadiazine.

the blood levels until the first subcutaneous dose was given. Nevertheless, it is clear that the intravenous injection of 4 gm. of calcium sulfadiazine, given as a 4% solution in distilled water, is an effective method for quickly establishing high levels of the drug in the blood. These blood levels may then be maintained and regulated by the judicious subcutaneous administration of different amounts of this compound.

Therapeutic Results. The essential data concerning 14 patients who were treated by the subcutaneous administration of calcium sulfadiazine for 24 hours, followed by sulfadiazine orally, are outlined in Table 1. These patients suffering from a variety of infections were

all acutely ill.* In each case the concentration of total sulfadiazine in the blood exceeded 7 mg. per 100 cc. within 3 hours after the first injection of drug. Thereafter the blood levels of sulfadiazine in these patients, during both parenteral and oral therapy, consistently tended to exceed the levels observed in control subjects after similar dosage. Domm and his associates[4] have suggested that this may be the result of impaired renal function during the height of illness. For the most part, total drug levels in the blood of these patients during treatment ranged from 7 to 15 mg. per 100 cc. In some cases, however, levels up to 20 mg. per 100 cc. were occasionally reached. Unless otherwise
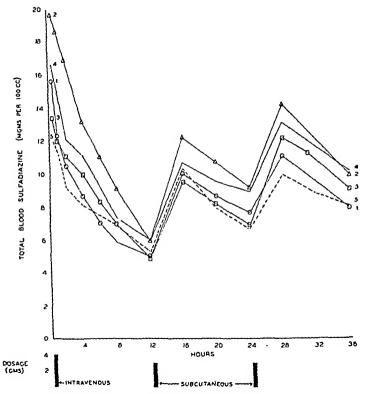
FIG. 2.—Concentrations of free sulfadiazine in the blood after an initial intravenous injection of calcium sulfadiazine, followed by two subcutaneous injections of the calcium salt.

noted, chemotherapy was continued for at least 48 hours after the patient's temperature had returned to normal or after unmistakable clinical signs of improvement had appeared. No severe toxic reactions attributable to the drug were observed in this series of patients, and there was an absence of nausea and vomiting. The skin eruption seen in 1 patient was confined to the face and upper extremities. It was macular in character and subsided promptly when the drug was discontinued. The microscopic hematuria exhibited by 2 patients was not sufficiently severe to warrant withdrawal of the drug.

* Bacteriologic data was obtained under Dr. Milton Levine, Director of the Bacteriology Laboratories, University Hospital.

Calcium Sulfathiazole. Only a few observations have been carried out with this compound in human subjects. Calcium sulfathiazole is a white, crystalline, odorless and slightly bitter compound. It is slightly less soluble than calcium sulfadiazine, but 10 times less alkaline than sodium sulfathiazole. Varying concentrations of solutions of calcium sulfathiazole are slightly more alkaline than comparable solutions of calcium sulfadiazine. The pH of a 5% aqueous solution of calcium sulfathiazole is 8.8.

The behavior of this compound following parenteral administration was observed in 5 adult males. These men ranged in weight from 53 to 73 kg. and were otherwise clinically comparable to the group which received trial injections of calcium sulfadiazine. Each injection was prepared from 4% solutions of calcium sulfathiazole dissolved in sterile distilled water at 80° C. and then cooled to 37° C. Each subject received an initial dose of 4 gm. intravenously followed in 12 hours by a subcutaneous dose of 3 gm. In 3 cases, further subcutaneous administration of sulfathiazole was discontinued because of redness, induration, and pain at the site of injection. Two patients received a second subcutaneous injection of 3 gm. of the drug 12 hours after the first injection with no untoward local symptoms. No generalized reactions resulted from the administration of calcium sulfathiazole by these methods. The sulfathiazole concentrations in the blood were one-half to two-thirds that obtained with calcium sulfadiazine under similar conditions.

Comment. The data presented here indicate that the calcium salt of sulfadiazine can be used safely and effectively in patients requiring parenteral chemotherapy. Solutions of this drug in distilled water are not strongly alkaline and have been administered subcutaneously as well as intravenously with no ill-effects in concentrations up to 4%. This allows considerable latitude in the regulation of dosage and in the maintenance of the desired blood levels. The rate of disappearance of drug from the blood after the injection of calcium sulfadiazine is not significantly different from that observed following the parenteral administration of comparable doses of sodium sulfadiazine. Thus, blood levels of a desired magnitude can be easily maintained by injections of calcium sulfadiazine at intervals of as much as 12 hours. The amount of drug and amount of fluid administered with each dose may be varied according to the needs of the individual patient.

It has long been known that the injection of ionized calcium salts may cause characteristic exudative lesions which provide peculiarly favorable cultural conditions for the growth of streptococci and anaërobic bacilli.[3,12] This phenomenon, called *kataphylaxis* by Bullock and Cramer,[3] apparently is not due to any increased virulence of the bacteria but to a reduction of local tissue resistance. In our series of patients, there were no instances of severe tissue reactions or superimposed infections at the site of injection of calcium sulfadiazine.

It has been reported that the intravenous injection of calcium salts into fully digitalized patients has precipitated sudden death.[10] How-

ever, Smith and his associates were not able to confirm this phenomenon experimentally.[17]   Calcium sulfadiazine has been administered intravenously to fully digitalized individuals without any ill-effects.

TABLE 1.—SUMMARY OF DATA FOR 14 PATIENTS WITH MISCELLANEOUS INFECTIONS TREATED WITH CALCIUM SULFADIAZINE ADMINISTERED SUBCUTANEOUSLY AND SULFADIAZINE GIVEN BY MOUTH

Case No.	Age (yrs.)	Sex	Treatment begun, day of disease	Diagnosis	Total dose of calcium sulfadiazine and sulfadiazine (gm.)	Toxicity	Response	Comment
1	33	M	17	Infectious arthritis	28	....	Good	M. tetragenus isolated from joint fluid
2	81	F	3	Bronchopneumonia	35	Erythematous skin eruption 7th day	Good	
3	68	M	2	Bacteremia (beta hemolytic streptococcus)	29	....	Good	
4	68	M	5	Lobar pneumonia (pn. Type I)	21	Crystalluria occasional red blood cells in urinary sediment	Death 4th day	Leukopenia on admission, initial blood culture positive (4900 organisms per cc.), subsequently sterile; 150,000 U. pn. Type I antiserum given; Francis test positive 2d day; autopsy: lobar pneumonia all lobes with empyema, right
5	64	F	1	Lobar pneumonia (pn. Type III)	22	....	Good	Left lower lobe involved; blood cultures sterile
6	60	F	3	Lobar pneumonia (pn. Type I)	25	....	Good	Left lower lobe involved; blood cultures sterile; mild right heart failure
7	62	M	4	Bronchopneumonia	19	Crystalluria, occasional red blood cells in urinary sediment	Good	
8	43	F	1	Bronchopneumonia	10	....	Death 25 hours	Thyroidectomy 2 days postoperative; pn. Type XXIII recovered from sputum; chronic alcoholism; autopsy: bronchopneumonia right lower lobe; left heart failure
9	58	F	2	Lobar pneumonia	27	....	Fair	Blood culture sterile; no pneumococci typed
10	35	M	47	?Blastomycosis; ?generalized coccidioidomycosis	26	Marked crystalluria	Death 16th day	Chemotherapy discontinued on 5th day; pulmonary involvement of all lobes; diffuse enteritis; no autopsy
11	10	M	4	Lobar pneumonia (pn. Type I)	66	....	Excellent	Initial blood culture, 5000 pn. Type I per cc.; subsequent cultures sterile; 100,000 U type specific antipneumococcus serum given; Francis test positive 2d day; entire left lung involved; sterile pleural effusion
12	46	M	10	Lobar pneumonia (pn. Type II)	22	...	Fair	Left lower lung involved; sterile pleural effusion; blood culture sterile
13	26	M	9	Lobar pneumonia (pn. Type I)	34	....	Fair	Empyema (pn. Type I) on right; surgical drainage; recovery uneventful
14	34	M	1	Lobar pneumonia (pn. Type XXVII)	29	....	Good	Left lower lobe involved; blood culture sterile

Preliminary investigations with the calcium salt of sulfathiazole indicate that its use may be accompanied by inflammation and necrosis, particularly in concentrations comparable to those used for calcium sulfadiazine. We do not recommend its clinical use. Data at hand do not permit us to draw any conclusions concerning the therapeutic efficiency of calcium sulfathiazole.

Summary. 1. Aqueous solutions of calcium sulfadiazine may be administered subcutaneously or intravenously in concentrations up to 4% with no ill-effects.

2. The pattern of absorption and excretion of calcium sulfadiazine, as measured by the rise and fall of drug level in the blood, does not differ significantly from that observed following the parenteral administration of comparable doses of sodium sulfadiazine.

3. Preliminary clinical experience indicates that calcium sulfadiazine administered subcutaneously is effective in establishing and maintaining adequate blood levels of drug in patients requiring parenteral chemotherapy.

4. Aqueous solutions of calcium sulfathiazole administered subcutaneously resulted in local inflammation.

5. It has been reported that aqueous solutions of sodium sulfadiazine in concentrations up to 5% may be safely administered subcutaneously. If these observations are confirmed, there appears to be no advantage in utilizing calcium sulfadiazine for this purpose.

REFERENCES

1. Billings, F. T., Jr., and Wood, W. B., Jr.: Bull. Johns Hopkins Hosp., **69**, 314, 1941.

2. Bratton, A. C., and Marshall, E. K., Jr.: J. Biol. Chem., **128**, 537, 1939.

3. Bullock, W. E., and Cramer, W.: Proc. Roy. Soc. London, **90**, 513, 1919.

4. Domm, A. H., Flippin, H. F., Reinhold, J. G., and Schwartz, L.: Arch. Int. Med., **69**, 51, 1942.

5. Finland, M., Strauss, E., and Peterson, O. L.: J. Am. Med. Assn., **116**, 2641, 1941.

6. Finland, M., Peterson, O. L., and Strauss, E.: New England J. Med., **225**, 601, 1941.

7. Flippin, H. F., Rose, S. B., Schwartz, L., and Domm, A. H.: Am. J. Med. Sci., **201**, 585, 1941.

8. Flippin, H. F., Rose, S. B., Schwartz, L., and Domm, A. H.: War Med., **2**, 284, 1942.

9. Fox, C. L., Jr.: Arch. Surg., **45**, 754, 1942.

10. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, p. 534, 1941.

11. Jorgenson, G. H., and Greeley, D. M.: J. Pediat., **21**, 325, 1942.

12. Kettle, E. H.: Lancet, **1**, 1169 and 1225, 1927.

13. Peterson, O. L., Strauss, E., Taylor, F. H. L., and Finland, M.: Am. J. Med. Sci., **201**, 357, 1941.

14. Plummer, N., and Ensworth, H. K.: Proc. Soc. Exp. Biol. and Med., **45**, 735, 1940.

15. Reinhold, J. G., Flippin, H. F., Schwartz, L., and Domm, A. H.: Am. J. Med. Sci., **201**, 106, 1941.

16. Sadusk, J. F., Jr., and Tredway, J. B.: Yale J. Biol. and Med., **13**, 539, 1941.

17. Smith, P. K., Winkler, A. W., and Hoff, H. E.: Arch. Int. Med., **64**, 322, 1939.

18. Taplin, G. V., Jacox, R. F., and Howland, J. F.: J. Am. Med. Assn., **114**, 1733, 1940.

19. Trevett, G. I., Nelson, R. A., and Long, P. H.: Bull. Johns Hopkins Hosp., **69**, 303, 1941.

20. Wheeler, C., and Plummer, N.: Ann Int. Med., **16**, 269, 1942.

THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH SULFAPYRAZINE*

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This paper is an amplification of a preliminary report[4] from this laboratory of the use of sulfapyrazine†[1,3] in pneumococcal pneumonia. Sulfapyrazine's antipneumococcal activity in experimental infections in mice has been shown to be at least as great as that of sulfadiazine and sulfathiazole, and its *in vitro* effectiveness greater than that of sulfadiazine but less than that of sulfathiazole.[6] Its absorption, excretion, and distribution in man resemble, in general, those of its isomer sulfadiazine.[2] Oral and parenteral administration of the drug to mice, rats, dogs, and monkeys[4,5] has indicated that its toxicity is low.

General Plan of Study. All the patients in this series were treated on the wards of the Cincinnati General Hospital. The patients were seen daily by one or more members of the group during the course of treatment and, when possible, examined by one member before sulfapyrazine therapy was instituted. The only criterion employed in the selection of cases was the diagnosis of "typical" pneumonia as determined by history, and physical examination or roentgenography. A blood culture and sputum sample were collected from each patient before the institution of chemotherapy; in a few instances, when sputum was not obtainable, exudate from a throat swab was inoculated into culture media. Treatment was never delayed, however, until the causative organisms were identified. When a blood culture showed growth, daily cultures were taken until at least 2 "negative" cultures had been reported; culture media contained 5 mg. per 100 cc. para-aminobenzoic acid. During the period from March 1, 1941 to June 30, 1942, about 40% of the adult patients suffering from pneumonia were treated with sulfapyrazine, while the great majority of the remainder received sulfathiazole. Antipneumococcal serum was given to those patients who did not respond promptly to chemotherapy, or, sometimes, to especially ill patients admitted in the fourth or fifth day of pneumonia.

Dosage of Sulfapyrazine. During the early part of this study, all patients were given an initial dose of 2 or 4 gm. followed by 1 gm. every 4 hours; all the drug was given orally. Later, it became our practice to administer the initial dose of 4 gm. intravenously, as a 5% solution of the sodium (monohydrate) salt, and to continue the maintenance dosage as before. Because of the appearance of instances of renal irritation in a few patients, the mainte-

nance dose was changed to 1 gm. every 6 hours; no patient receiving this dose showed signs of renal toxicity. The therapeutic efficacy of the drug appeared to be just as great with the smaller total dose. Sulfapyrazine was administered routinely until the rectal temperature remained below 99° F., for 48 hours; an average total dose of 30.4 gm. was given to the patients in this series.

Type Distribution. The sulfapyrazine-treated group comprised 105 cases, whose type distribution is shown in Table 1. Types I, II, III, V, VII and VIII accounted for more than 70% of the total; in 12 instances, no etiologic diagnosis could be made by blood or sputum culture. Twenty-four (23%) of the patients had bacteremia at the time chemotherapy was instituted.

TABLE 1. — DISTRIBUTION OF PNEUMOCOCCUS TYPES

Type	No. of patients	No. of deaths	No. of patients with bacteremia
I	22	0	8
II	9	0	3
III	8	0	2
IV	2	0	0
V	9	1	4
VI	1	0	0
VII	15	0	1
VIII	9	0	2
IX	1	0	0
XI	1	0	0
XII	1	0	0
XIII	1	0	0
XIV	3	1	1
XVI	2	1	1
XVIII	2	1	1
XIX	2	0	0
XXIV	1	0	1
XXVII	3	0	0
XXXIII	1	0	0
Untyped	12	0	0
Totals	105	4	24

TABLE 2. — MORTALITY IN PNEUMOCOCCAL PNEUMONIA, CINCINNATI GENERAL HOSPITAL MARCH 1941-JUNE 1942

	Drug	
	Sulfathiazole, July 1941–June 1942	Sulfapyrazine, March, 1941–June 1942
All cases	133	105
Number of deaths	9	4
Mortality, %	7	4
Non-bacteremic cases	107	69
Number of deaths	4	0
Mortality, %	4	0
Bacteremic cases	26	24
Number of deaths	5	4
Mortality, %	19	17

Results of Treatment. (See Table 1.) All of the patients, except 4, recovered. The 4 fatal cases occurred in patients with bacteremia. Two of these patients received serum in fairly large doses in addition to the sulfapyrazine, while a third received human plasma. With one exception, the fatalities occurred in patients over 50 who gave evidence of degenerative disease. For purposes of comparison, the mortality figures for sulfathiazole-treated pneumonia at the Cincinnati General Hospital during the same period are shown in Table 2; none of the patients

receiving sulfathiazole received serum.   It can thus be seen that there was no striking difference in the curative value of the two drugs.

Even though sulfapyrazine is in no sense an antitoxic substance, it seemed to share the property of certain of the other sulfonamides of diminishing the signs of "clinical toxicity" so frequently associated with pneumococcus pneumonia.   This improvement in clinical condition was usually apparent in 12 to 24 hours and was apparently independent of the patient's temperature.   A critical fall of temperature occurring after the administration of the drug was noted in 45% of the non-bacteremic cases and in only 16% of the recovered bacteremic patients; similar incidences might be expected in untreated patients. The details of the fatal cases are appended below.

The celerity with which blood cultures from bacteremic patients may become "negative" under sulfonamide treatment is striking.   This property of sulfapyrazine was exemplified in 2 patients with 350 and 680 colonies per cc., respectively, of Type V pneumococci; within 24 hours the blood culture showed growth only in the flasks and on subsequent examinations they were sterile.   In another case, the blood culture showed countless colonies of Type XVIII pneumococci before treatment, but was sterile 16 hours after an intravenous injection of 4 gm. of sodium sulfapyrazine.   No patient in this series developed a purulent complication of pneumonia under treatment.   However, 2 patients were admitted with focal purulent complications: 1 with infected pleural fluid containing pneumococcus I, and another with pyarthrosis of the knee and sternoclavicular joints due to pneumococcus V.   The pyarthroses disappeared completely without requiring surgical drainage, but the empyema ultimately required rib resection.

Drug Toxicity.   There was no proved instance of sulfapyrazine causing a deleterious effect upon the central or peripheral nervous system. In 3 cases, delirium occurring during treatment was thought by some observers to be due to the drug, but readministration of the drug, in similar dosage, did not cause a repetition of the delirium in these patients.   There was 1 instance of nausea and vomiting and 2 instances of fever which may have been due to the drug.   One patient developed a morbilliform eruption during the course of treatment, but the rash could not be duplicated during convalescence, when sulfapyrazine treatment was reinstituted.   No cyanosis or jaundice associated with chemotherapy was seen.

The major toxic effects of sulfonamides on the red and white blood cells were not encountered among patients of this series.   In 1 instance there was a decrease in the white blood cell count from 10,900 to 2700, with 43% polymorphonuclears, observed.   The drug was readministered during convalescence after the total count had returned to normal but no effect was noted, either quantitatively or qualitatively.

In 5 of 57 patients given 6 gm. of sulfapyrazine a day, an elevation of the blood urea nitrogen, associated with pain in the flank, hematuria, and oliguria, occurred during treatment; in no instance did anuria supervene.   In 2 cases, the blood urea nitrogen rose from 18 mg. per 100 cc. and 21 mg. per 100 cc., respectively, on admission, to 49 mg. per 100 cc. and 61 mg. per 100 cc., and in the third case from 42 mg.

per 100 cc. to 90 mg. per 100 cc.   In 2 other cases, where determinations of the blood urea nitrogen were not made on admission, elevations to 50 mg. per 100 cc. and 143 mg. per 100 cc. were discovered later. No patient developed any clinical signs of uremia, and in every instance the blood urea nitrogen returned to normal following discontinuance of the drug and proper attention to fluid intake.   Among 44 patients treated with 4 gm. a day, no significant signs of renal toxicity were seen, though a few red blood cells were discovered microscopically in 6 cases.

Summary of Fatal Cases.   CASE 1.   This 31 year old negress worked until the day before admission to the hospital.   She gave a typical history of pneumococcal pneumonia of 24 hours' duration.   On admission she was acutely ill with a temperature of 105.8° F., pulse 130, respirations 44, and blood pressure 130 systolic and 70 diastolic.   There were classical signs of consolidation of the left upper lobe, but the lungs were otherwise clear.   The white blood cell count was 5000 with 80% neutrophils.   The red blood cell count was 3,700,000, hemoglobin 12.5 gm.   The urine was normal.   The blood urea nitrogen was 21 mg. per 100 cc.

She was given 4 gm. of sodium sulfapyrazine intravenously 1½ hours after admission.   Six hours later the blood pressure had fallen to 70 systolic, and moist râles were present throughout the lungs.   She died a few minutes later, despite efforts at resuscitation.   Her total dose of sulfapyrazine was 5 gm. Type V pneumococci were later recovered from a culture of a throat swab, and from the broth of the admission blood culture, though no colonies appeared on the agar plates.   Permission for necropsy was refused.

CASE 2.   A 68 year old white woman, afflicted with asthma and chronic bronchitis for the previous 8 years, was admitted to the hospital with pneumonia of 7 days' duration involving the entire right lung.   She was cyanotic and covered with sweat.   The extremities were ice-cold.   The temperature was 101.6° F., the pulse 120, respirations 28, and the blood pressure 80 systolic and 60 diastolic.   Moist râles and rhonchi were heard over the entire chest. The white blood count was 14,400, and the urine contained albumin.   The admission blood culture was positive for Type XIV pneumococcus.

She was given 5 gm. of sodium sulfapyrazine intravenously, and supportive treatment which included oxygen, intravenous plasma, and hourly intravenous injections of paredrine.   Despite these measures, the pulse became weaker and weaker, and the systolic blood pressure dropped to 40 mm. Hg.   She died 17 hours after admission.

Autopsy revealed gray hepatization involving the right upper and middle lobes, and patchy involvement of the right lower lobe, and slight edema of the left lung.

CASE 3.   A 55 year old white man was admitted in the 5th day of pneumonia of the right middle and lower lobes, due to Type XVI pneumococcus. He was a chronic alcoholic who had lost 55 pounds in the preceding year and a half, and had signs of cardiac decompensation.   On admission the temperature was 101.8° F., pulse 132, respirations 28, and blood pressure 110 systolic and 70 diastolic.   He was somewhat irrational.   The skin was icteric, and the liver was enlarged and nodular.   The white blood cell count was 3000, with 74% young neutrophils.   Bile and albumin were found in the urine. The blood urea nitrogen was 23 mg. per 100 cc.   The blood culture contained 376 colonies of Type XVI pneumococci per cc.

Four gm. of sulfapyrazine were administered by mouth, and 5 gm. more during the next 12 hours.   Twelve hours after admission he was given 200,000 units antipneumococcal rabbit serum, but he grew steadily worse, and died 2 hours later.   Permission for necropsy was refused.

CASE 4.   A 75 year old negro was admitted to the hospital on the 7th day of pneumococcus XVIII pneumonia of the left upper lobe.   For 5 months previously he had suffered from cardiac decompensation.   On admission his

temperature was 103° F., pulse 112, respirations 42, and blood pressure 75 systolic and 50 diastolic. The pupils were irregular and reacted poorly to light, the heart was enlarged, and coarse râles were present throughout both lung fields. The white blood cells numbered 28,500; the specific gravity of the urine was 1.024, and a few white blood cells were seen in the sediment. The blood urea nitrogen was 85 mg. per 100 cc. The admission blood culture contained countless colonies of Type XVIII pneumococci.

Four gm. of sodium sulfapyrazine were given on admission, and 200,000 units of antipneumococcal rabbit serum 16 hours later. A blood culture taken just before administration of the serum was sterile. Two more grams of sulfapyrazine were given by mouth, and supportive therapy administered in the form of oxygen, aminophyllin, and the plasma from 1 liter of whole blood. Nevertheless, the systolic blood pressure failed to rise above 100, and the patient died 30 hours after admission.

Autopsy revealed gray hepatization of the left upper lobe, severe toxic changes in the heart and kidneys, fatty infiltration of the liver, and fusiform syphilitic aneurysm of the ascending aorta.

Summary. The results of the use of sulfapyrazine in the treatment of 105 cases of "typical" pneumonia are presented. The drug bears out its original promise of being an effective agent in the treatment of pneumococcal pneumonia, for the mortality in this series was only 4%. The mortality among the 24 bacteremic cases was 17%.

The only important toxic effect of the drug was upon the kidneys. Evidence of transient renal damage was found in 9% of the patients treated with 1 gm. every 4 hours. In patients treated with 1 gm. every 6 hours, the only manifestation of renal injury was the occasional microscopic finding of small numbers of red blood cells. The incidence of renal irritation of sulfapyrazine in larger series of cases should be investigated.

The other toxic effects commonly produced by sulfonamide drugs appeared but rarely in this series. One morbilliform rash and 1 instance of nausea and vomiting were believed to be due to sulfapyrazine.

• REFERENCES

1. ELLINGSON, R. J.: J. Am. Chem. Soc., 63, 2524, 1941.
2. HAMBURGER, M., JR., RUEGSEGGER, J. M., BROOKENS, N. L, and EAKIN, E.: AM. J. MED. SCI., 204, 186, 1942.
3. RAIZISS, G. W., CLEMENCE, L. W., and FRIEFELDER, M.: J. Am. Chem. Soc., 63, 2739, 1941.
4. RUEGSEGGER, J. M., HAMBURGER, M., JR., TURK, A. S., SPIES, T. D., and BLANKENHORN, M. A.: AM. J. MED. SCI., 202, 432, 1941.
5. RUEGSEGGER, J. M., and HAMBURGER, M., JR.: Unpublished observations.
6. SCHMIDT, L. H., RUEGSEGGER, J. M., SESLER, C. L., and HAMBURGER, M., JR.: J. Pharm. and Exp. Ther., 73, 468, 1941.

STATUS OF SULFONAMIDE THERAPY IN MALARIA

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WITH the onset of the war in the Pacific it became evident that the supply of quinine and its derivatives to the Allied Nations would, to

say the least, become drastically curtailed. Subsequently, and even prior to December 7, 1941, physicians and other interested investigators began to consider departures in anti-malarial therapy radically different from the tried and accepted quinine salts. It had long been accepted that there was no ideal anti-malarial drug, quinine most nearly approaching the ideal and being sufficiently satisfactory to cool the ardor of those who would have sought further. Out of the circumstances culminating in the loss of the East Indies and the concomitant loss of 90% of the world's supply of quinine came further impetus for investigators in their search for the ideal and, indeed, any effective and readily available anti-malarial drug.

The problems of oiling and draining bodies of stagnant water, which serve as breeding places, while capable of solution in certain malarious areas, loom as utterly impossible of solution in others. It is therefore obvious that complete destruction of the Anophelini may never be accomplished. Since it is impossible to remove the vector from the cycle, the next most desirable procedure would appear to be the eradication of human reservoirs of infestation. Theoretically, the simultaneous screening of all infested individuals until biologic cure is attained would needs be considered as one method for accomplishing this end. Practically, this consideration would be discarded at once. It would be about as easy as eradicating syphilis by segregating all syphilitics and treating them simultaneously until all were arrested or cured. The remaining alternative would be the employment of one or more drugs, which would be considerably more effective than the venerable but epidemiologically, at least partially, ineffective quinine derivatives. In order to improve upon the malaria situation as we now find it, the new drug or drugs should be relatively inexpensive, easily accessible, not too toxic, and capable of ridding the blood stream of parasites within a relatively short time. To attain the maximum results, even with such a drug available, diagnostic facilities and the means of distribution and administration of the drug would also require further development. Withal, the new treatment should not of necessity require a long enough treatment period to try the patience of the individuals taking it. The long treatment period required with the use of quinine and the resulting desertion of the treatment schedule by patients has been one of the chief objections to the use of this drug. However, since December 7, 1941, any discussion of the defects of quinine would appear to be academic.

Sulfathiazole in Therapeutic Vivax and Malariæ Malaria. In January of 1942, the author treated a case of therapeutic quartan malaria, a neurosyphilitic, with sulfathiazole and independently found that a definite anti-malarial quality was possessed by the drug. This case, No. 13027, had had several paroxysms over 103° F., rectal. Between January 6 and 9, 1942, he was given 2 gm. of sulfathiazole q.i.d. (q. 4 hr.) for 24 hours followed by 1 gm. q.i.d. There were paroxysms on January 8 and 11. These were followed by two slight reactions of less than 102° F., and then a paroxysm with 104° F. on January 25. He was completely free of even low grade fever from January 13 to 19.

On January 25, the regular quartan pattern was resumed and was subsequently terminated with quinine sulfate. On February 14, 1942, Case 13065, who also had therapeutic quartan malaria, was begun on sulfathiazole, 1.5 gm. q.i.d. (q. 4 hr.), for 2 days and followed by 1 gm. t.i.d. for 2 days. From the time of the beginning of the sulfathiazole schedule there were no further febrile reactions and after discontinuation of the medication the patient remained fever-free until February 26, 1942, on which day there was a temperature elevation to 101.5° F. On March 1, there was a temperature of 102.6° F. Quinine therapy was begun on March 2, 1942. The next day there was a paroxysm with elevation to 104.2° F. There were no further febrile reactions. From observations in these 2 cases it was concluded that, while sulfathiazole demonstrated some anti-malarial action although failing to permanently interrupt the malaria course in either case, other members of the sulfonamide series should be investigated. Accordingly, a study of the effects of sulfadiazine in therapeutic quartan malaria was undertaken. Sulfadiazine was selected on account of its extremely low toxicity and its broad margin of safety.

In November, 1941, Schwartz et al.[5] published results of their work with sulfathiazole as an anti-malarial in 9 neurosyphilitics undergoing therapeutic tertian malaria. The patients were allowed to have from 3 to 15 chills before sulfonamide medication was begun. Three gm. was the initial dose and this was repeated in 4 hours. Thereafter 1. gm. was given every 4 hours for a total dosage of 25 to 50 gm. Chills and fever ceased in every patient after sulfathiazole but the blood was cleared of plasmodia in only 5 of the 9 cases. One of these suffered a relapse 15 days after discontinuation of sulfathiazole therapy. After a period of 90 days there had been no sign of relapse in the other 4. The remaining 4 patients, whose blood could not be cleared of plasmodia, all experienced clinical relapses in from 12 to 20 days after the chemotherapy was discontinued. There were no serious toxic manifestations in any of the 9 patients.

Work of Coggeshall and others. As early as 1938 sulfanilamide was employed by Coggeshall[1] in the treatment of *P. knowlesi* malaria in *Macacus rhesus* monkeys. In this type of malaria sulfanilamide effected complete sterilization of the blood of the test monkeys. His experience in this connection led him to the use of sulfanilamide in human malaria but here he found it without effect. On September 27, 1941, Coggeshall, Maier, and Best[2] published their results of the treatment of various types of malaria with promin (sodium P,P′-diaminodiphenylsulfone N,N′-didextrose sulfonate) and with sulfadiazine (2-sulfanilamido-pyrimidine). Seventeen cases were treated with promin, of which 12 were vivax and 5 falciparum infestations. In the vivax cases the time interval required for disappearance of fever varied from immediate to 6 days with an average of $2\frac{5}{6}$ days. Of these 12 cases, plasmodia persisted in the blood in 4 and required from 1 to 5 days for their disappearance in the remaining 8 cases with an average of $3\frac{2}{3}$ days. The treatment periods varied from 3 to 4 days in each case and the total dosage varied from 5 to 40 gm. In the falciparum cases, 5 in

number, there were none in which plasmodia persisted. Gametocytes persisted in 1 case for 10 days. In the remaining 4 all parasites disappeared in a period of 2 days. The duration of the attack in all 17 cases before treatment was begun varied from 1 to 14 days, averaging $5\frac{1}{17}$ days. Promin was then used in several patients who had therapeutic malaria but results here were inconclusive. One of these patients experienced a resumption of paroxysms. Four of them were treated with promin for 3 days after having had 10 paroxysms each. Blood smears became negative and fever disappeared within 2 days. There was no recurrence of symptoms or parasites for 6 days. The patients then received the routine course of quinine. From an experimental point of view the quinine should not have been administered until a considerably later period, if at all, in order to have determined
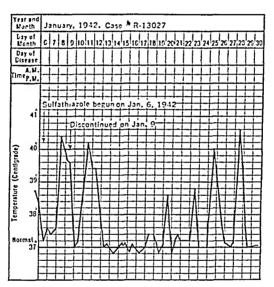
FIG. 1.—Graphic representation of effect of 3 days treatment of Case 13027, a case of therapeutic quartan malaria. Sulfathiazole.

whether relapse would have occurred. If the patients were to have been released from observation within a short time the administration of quinine would have been proper since it had not been established that promin would cure therapeutic malaria and that paroxysms would not have resumed subsequent to release from observation.

These investigators also studied the effect of sulfadiazine on acute naturally acquired malaria. Thirteen cases were studied of which 7 were vivax infestations, 5 falciparum, and 1 malariæ. The number of days of duration of the attack before treatment had begun varied from 1 to 18 with an average of $4\frac{1}{3}$ days. In 1 case of vivax and in 2 cases of falciparum infestation no effects were observed. In the remaining 10 cases fever disappeared in from $\frac{1}{2}$ to 3 days and plasmodia disappeared from the blood in from 1 to 5 days. The treatment period was the same in all cases and was for 6 days, 6 gm. being given on the

first day and 4 gm. daily for the remaining 5 days. From the fact that in 1 case 5 days were required for the parasites to disappear, it is possible that a treatment period of even more than 6 days may have been indicated.

The conclusion of these authors was that "at present there are no reasons for giving the drugs (sulfonamides) in preference to quinine or atabrine for the treatment of malaria, and they should be regarded only as important substitutes." In comment on this conclusion it should be pointed out that this paper was published before the East Indies were occupied by the Japanese and our supply of high grade quinine cut off. If the sulfonamides are to be regarded as important substitutes for quinine, it is apparent that now is the time to use them for that purpose.
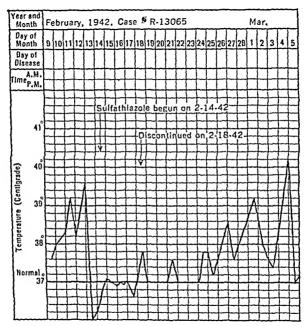
FIG. 2.—Effect of 4 days treatment of Case 13065, also a case of therapeutic quartan malaria. Sulfathiazole was also used here.

Relative Numerical Importance of Tertian and Quartan Therapy. The use of quartan malaria for therapeutic purposes has become much more general in the past few years, especially in the Pacific Coast area where it is used almost to the exclusion of tertian. Long range results of malaria therapy in neurosyphilitics are said to be slightly better with tertian than with quartan malaria but due to the milder course of the disease and to the smaller number of complications with corresponding lowering of mortality rates in the latter,[3] quartan therapy is becoming ever more popular with conservative neurosyphilologists. Results of the study of the effects of sulfadiazine in therapeutic quartan malaria (to follow) would therefore appear to be of greater import than would have been the case a decade ago.

Therapeutic tertian malaria, which has a marked tendency to spontaneous remission, requires a treatment period of only about 10 days

with relatively light quinine dosage. Obviously then, it does not constitute a problem of considerable dimensions. Moore,[4] who has had an enormous experience with therapeutic malaria, states that he has never seen a relapse in artificially induced tertian malaria following a proper quinine course. In contrast, therapeutic quartan malaria is characterized by a fairly high incidence of relapses and requires considerably more energetic treatment than does tertian.

The strain of quartan employed in our series has been in constant use for a period of more than 10 years and has long since become asexualized. It produces a very regular quartan fever pattern and spontaneous remissions never occur in it except in patients who have had natural or a previously induced course of therapeutic quartan malaria. It was considered ideal for a study of the effects of sulfadiazine on asexual artificially induced quartan malaria. It was also considered favorable that the patients under study could be kept under observation for a comparatively long time and that this would aid materially in determining the rate of relapse after treatment.

Sulfadiazine Therapy.   Untoward Reactions.   As stated above, sulfadiazine was selected for our work, from the sulfonamide field, largely on account of the low toxicity of the drug. Toxic reactions of any importance are apparently rare. One of the most common side effects, of a mild nature, is a state of mild confusion and cloudiness of sensorium which clears rapidly upon withdrawal of the drug and results in no permanent detrimental condition. Coggeshall et al.[2] comment on a case of malaria treated by them with sulfadiazine in which fever developed as a result of the medication and ceased at once upon its discontinuation. In our first series, of 10 malaria cases, treated with this drug there was 1 case of severe emesis which became active with each dose administered. Evacuation of the stomach occurred each time within a few minutes after the drug was taken. Even so, however, a sufficient amount of it was retained to clear the blood of plasmodia for a period of 39 days and to cause disappearance of febrile reactions. Although it is conceded that routine administration of sodium bicarbonate with sulfadiazine is not a preferred procedure, it has been our practice to give it when nausea developed during the course of medication. Accordingly, sodium bicarbonate was begun in this case but failed to check the vomiting. Finally the withdrawal of the sulfonamide became necessary in order to control it. In view of the emesis and of the consequent loss of a large proportion of the sulfadiazine, this case was not counted a relapse with sulfadiazine therapy.

No renal disturbances at all were noted in the above series. Wright and Kinsey[6] discuss cases of anuria resulting from the use of the drug. They state that it is their opinion that this will not occur if the dosage is kept at or under 4 gm. daily. In our work, with the exception of the first 24 to 48 hours during which larger doses were given for the purpose of building up blood levels, daily dosages have been 4 gm. or less. We are now following their suggestion of searching for the combined presence of sulfadiazine crystals and red blood cells in the urine specimens which we examine on all cases under sulfadiazine therapy. They

state that the presence of this combination indicates crystalline concretions in the ureters and constitutes an indication for discontinuation of the treatment schedule.

With the exception of the emesis case above described, no other toxic manifestations were observed in this series.

Technique of Administration. A set of standard conditions was established for the 10 cases constituting series No. 1. All patients were kept at bed rest but were allowed bathroom privileges. Otherwise they were kept continuously in bed and were served their meals there. No other medication was given during the sulfonamide course except sodium bicarbonate in the 1 case above discussed. The usual routine in our neurosyphilis clinic of 4 intravenous injections of mapharsen following the termination of malaria was abandoned on account of the anti-periodic effect of this trivalent arsenical. This was done to enhance the evaluation of the sulfonamide therapy. Specimens of urine were sent to the laboratory for examination every other day and daily if the indication arose.

A number of different treatment schedules were used in the several cases treated. The general principle of heavier dosages on the first day or two followed by a reduced maintenance dosage, was adhered to in all cases. In series No. 1 the treatment periods varied from 4 to 8 days with four patients under treatment for 4 days, two for 5 days, two for 7 days, and two for 8 days. The average number of treatment days was 5.6. Total dosages varied from 24 to 40 gm., four patients receiving 24 gm., two 28, two 36, and two 40 gm.; average amount 30.4 gm. Sulfadiazine was used in all cases except one in which sulfathiazole was employed due to the complicating development of an urinary tract infection. In series No. 2, comprising 4 cases, treatment periods were 9 days in 1 case and 10 days in each of the other 3 cases. Here total dosages varied from 44 to 48 gm. The purpose of dividing treated cases into two series was to compare efficacy of longer treatment periods with that of shorter periods but since the number of cases in series No. 2 was so small such a comparison would have been of no statistical value. Relapse rates were therefore computed from the total number of cases making up the two series. Incidentally, the rates in the two series were approximately the same.

All patients were protected from exposure to direct sunlight.

Results. The treatment periods under the sulfonamides were uneventful in the great majority of the cases treated. One patient suffered severe emesis as a result of his sulfadiazine therapy. Vomiting was not alleviated by alkalization. It was felt that he retained only a small amount of the drug from each dose and he was therefore not included in the group of patients from which the relapse rate was computed. All others in both series were included.

In the 13 cases which were considered suitable for the study there were 3 relapses, or a relapse rate of 23%. In Case 13148, one of the 3 relapses, there was no recurrence of symptoms but there was a reversion of blood smears to positivity. This relapse occurred 79 days after completion of the sulfadiazine course. A course of 4 days sulfa-

diazine therapy at the time of the relapse caused the parasites to disappear from the peripheral circulation and to this date, 150 days since, there has been no symptomatic relapse and plasmodia have not reappeared in the blood. In Case 13206 there was a symptomatic relapse 33 days after completion of the sulfadiazine course and plasmodia were found to be present in the blood. At the beginning of the second course of sulfadiazine, then begun, emesis occurred with each dose and the drug was abandoned in favor of quinine sulfate. Of the 4 cases constituting series No. 2, one (Case 13297) suffered symptomatic relapse with reappearance of plasmodia in the blood 44 days after sulfadiazine therapy. An additional course of sulfadiazine was begun at once and continued for a period of 4 days. Abatement of symptoms and disappearance of plasmodia from the blood was the result. At this time, 68 days since, there has been no recurrence of fever and several blood smears have been negative.

FIGURE 3—SERIES No. 1

Case No.	Type malaria used	Drug used	Days, treatment	Amount, gm.	Pre-treatment smears	Smears after treatment	Days since treatment	Relapse	Toxic reaction
13165	Q	Diazine	7	36	Pos.	Neg.	239	No	No
13148	Q	Diazine	8	40	Pos.	Neg.	248	Yes	No
13194	Q	Diazine	7	36	Pos.	Neg.	227	No	No
12503	Q	Diazine	5	28	Pos.	Neg.	198	No	No
13190	Q	Thiazole	8	28	Pos.	Neg.	264	No	No
13206	T	Diazine	5	28	Pos.	Neg.	204	Yes	Yes
12882	Q	Diazine	4	24	Pos.	Neg.	190	No	No
12501	Q	Diazine	4	24	Pos.	Neg.	179	No	No
13247	Q	Diazine	4	24	Pos.	Neg.	186	No	No

Ten patients originally constituted this series but 1 was omitted as explained in text. Patients in this series received from 4 to 8 days of sulfonamide treatment while those in series No. 2 received either 9 or 10 days of treatment each. It was intended to run the two series in order to compare efficacy of shorter and longer courses but small number of cases in series No. 2 would not permit statistical comparison of any value. Relapse rates are computed on basis of total number of patients in the two series.
T = Tertian.   Q = Quartan.

FIGURE 4.—SERIES No. 2

Case No.	Type malaria used	Drug used	Days, treatment	Amount, gm.	Pre-treatment smears	Smears after treatment	Days since treatment	Relapse	Toxic reaction
13300	Q	Diazine	10	48	Pos.	Neg.	124	No	No
13297	Q	Diazine	9	44	Pos.	Neg.	116	Yes	No
13323	Q	Diazine	10	46	Pos.	Neg.	73	No	No
13345	Q	Diazine	10	46	Pos.	Neg.	70	No	No

This series consisted of 4 patients. Treatment periods were 9 to 10 days and the total dosage of sulfadiazine was from 44 to 48 gm. There was 1 relapse in the 4 cases.
T = Tertian.   Q = Quartan.

It will be noted in the accompanying tables that in no case did the drug fail to bring about a disappearance of plasmodia from the blood smears. Likewise, no patient failed to obtain complete symptomatic relief from this medication. Our experiences with sulfadiazine in the cases which suffered relapses, as well as those which did not, has led us to the practice of routine use of the drug in all cases but the exceptional ones in which it is not tolerated. The length of time required for control of paroxysms by use of sulfadiazine was found in our series to closely parallel that found by Coggeshall and co-workers[2] in a series of naturally acquired malarial cases.

It is conceivable that the implication of these observations could be of military significance, in that army personnel finding themselves in

isolated positions could employ this drug when contracting malaria. (We are in receipt of advice from local military-medical authorities that sulfadiazine tablets are replacing the sulfanilamide tablets which have been carried on the persons of soldiers in the field.)

The question of why some patients are permanently cured of the disease while others have relapses may possibly be answered at a later date by sulfadiazine blood level studies. So far as we have been able to learn this has not yet been undertaken. The above-described cure of relapsed cases with a second course of the drug should lead to further studies along this line and elicits the possibility of a treatment schedule which would employ a second course initially instead of only after a relapse. Both of these considerations are being investigated in cases currently under treatment by the author.

Summary. 1. The need for a new and effective anti-periodic are described, along with present obstacles in the use of quinine derivatives.

2. The author's independent discovery of the anti-malarial action of sulfadiazine, and of sulfathiazole as a point of predication, is considered.

3. A résumé of the work of Schwartz *et al.* indicates that sulfathiazole in their hands was effective as an anti-malarial in only about 50% of the cases.

4. The work of Coggeshall *et al.* with the sulfonamides, promin and sulfadiazine, in the treatment of naturally acquired and therapeutic malaria is reviewed. Results in the latter were inconclusive but were indicative that sulfonamides possessed an anti-malarial action in both naturally acquired and therapeutic malaria. Sulfanilamide was found to be without effect in human malaria.

5. Quartan malaria is used therapeutically much more widely than formerly, so that positive treatment results with sulfadiazine have also become more important.

6. Toxic and other untoward treatment complications in the use of sulfadiazine are described along with precautions to be observed.

7. Technique of administration and treatment schedules are discussed. The author's treatment results are described and tabulated.

8. Possible military significance of the author's treatment results is discussed.

Conclusions. 1. Sulfadiazine is an effective anti-malarial.

2. It is exhibited with a minimum of toxic reaction and is therefore taken by patients with less reluctance than is quinine.

3. The relapse rate, employing our dosage schedules and in therapeutic quartan malaria, has been established at 23%. The amount of treatment used appeared to have no relation to the relapse rate. Patients suffering relapses had had 5, 8, and 9 days of treatment respectively.

4. Relapses are controlled by a second course of sulfadiazine. No patient has had a second relapse.

5. The anti-malarial action of sulfadiazine could be used to advantage by the military in malarious areas.

REFERENCES

1. COGGESHALL, L. T.: Am. J. Trop. Med., 18, 715, 1938.
2. COGGESHALL, L. T., MAIER, J., and BEST, C. A.: J. Am. Med. Assn., 117, 1077, 1941.
3. JOHNSON, C. E., JR.: Med. Bull., 19, 22, 1942.
4. MOORE, J. E.: The Modern Treatment of Syphilis, 2d ed., p. 385.
5. SCHWARTZ, L., FURST, W., and FLIPPIN, H. F.: Am. J. Hyg., 34, 141, 1941; Abstr., J. Am. Med. Assn., 118, 559, 1942.
6. WRIGHT, D. O., and KINSEY, R. E.: J. Am. Med. Assn., 120, 1351, 1943.

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PROTHROMBIN STUDIES USING RUSSELL VIPER VENOM

VI. THE STABILITY OF THE THROMBOPLASTIC-LIKE ACTIVITY OF RUSSELL VIPER VENOM UNDER VARIOUS CONDITIONS OF STORAGE

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THE use of Russell viper venom as a thromboplastic-like substance in Quick's test[4] for prothrombin clotting time has been advocated on the grounds that it possesses several advantages over thromboplastin derived from rabbit brain. Essentially the same relative results have been obtained with both thromboplastic agents.[3] The commercially available venom is convenient, quite uniform within and between batches, and, as originally packaged, stable for at least 5 years.[1] The present study deals with the stability of venom solutions under various conditions of storage.

Method. Considerable amounts of 2 batches of venom were secured.† A portion of each batch of venom was dissolved in water to make a concentration of 1 to 10,000. A water solution of venom from many ampoules of the same batch was pooled and then divided into 4 portions and stored as follows: 2 portions, 1 tightly stoppered and 1 lightly stoppered (the opening being sufficiently small to prevent appreciable evaporation and consequent concentration of the venom but sufficiently large to permit the access of air), were kept in the laboratory at room temperature, and the 2 other portions, 1 stoppered and the other lightly stoppered, were kept in a refrigerator.

At 2-week intervals throughout a period of 18 weeks, all 4 samples were tested for thromboplastic activity by determining the prothrombin clotting time of samples of normal venous blood. The method consisted in adding venom solution to oxalated plasma and then adding calcium chloride. The time required for the formation of fibrin flecks is the prothrombin clotting time.[2] All determinations were done in triplicate.

The balanced experimental design as indicated in the tables possessed several advantages. In addition to revealing the effects of storage conditions, com-

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* On active service with the Armed Forces of the United States.
† Russell Viper Venom ("Stypven") was supplied by Burroughs Wellcome & Co. (U. S. A.) Inc., New York, N. Y.

TABLE 1. EFFECTS OF STORAGE CONDITIONS ON THE THROMBOPLASTIC ACTIVITY OF SOLUTIONS OF RUSSELL VIPER VENOM* AS MANIFESTED IN THE CLOTTING TIMES OF NORMAL HUMAN BLOOD

Batch No. 191A—Expiration date: March 4, 1941

Interval	Control (freshly prepared each time) H (sec.)	P	Refrigerated (tightly stoppered) H (sec.)	P	Refrigerated (lightly stoppered) H (sec.)	P	Room temperature (tightly stoppered) H (sec.)	P	Room temperature (lightly stoppered) H (sec.)	P
Freshly prepared	19.8, 20.8, 20.4	17.2, 17.0, 17.4	19.8, 20.8, 20.4	17.2, 17.0, 17.4	20.2, 20.4, 19.6	17.2, 17.6, 17.6	20.5, 21.0, 21.2	16.0, 16.2, 16.6	19.6, 19.8, 20.2	16.0, 16.2, 17.0
1 week	17.5, 17.8, 18.2	18.2, 19.0, 19.0	19.4, 20.0, 20.4	21.0, 21.6, 22.0	20.2, 20.4, 20.6	19.5, 20.3, 20.5	17.8, 18.0, 18.5	20.0, 21.0, 20.8	20.0, 20.5, 20.6	23.0, 23.2, 23.3
2 weeks	17.5, 17.8, 18.2	18.1, 18.6, 18.7	15.9, 16.4, 16.2	19.0, 20.0, 20.0	17.9, 17.1, 17.5	17.0, 17.1, 17.9	16.0, 16.2, 16.7	17.6, 18.2, 17.6	16.0, 16.1, 16.9	16.8, 16.4, 16.5
4 weeks	17.5, 17.8, 17.6	17.0, 17.8, 17.5	16.8, 17.0, 17.1	16.8, 17.0, 17.4	17.1, 17.1, 16.9	16.5, 16.7, 16.8	16.5, 17.0, 17.1	16.5, 17.0, 16.4	16.1, 16.0, 16.4	17.2, 17.4, 17.0
6 weeks	19.5, 20.0, 20.0	19.2, 19.0, 19.4	19.4, 20.1, 20.4	20.2, 20.4, 20.6	20.0, 19.6, 20.4	21.8, 21.6, 22.0	20.1, 20.6, 19.5	18.9, 18.7, 19.2	21.0, 20.8, 21.2	24.0, 23.2, 22.8
8 weeks	21.8, 21.0, 21.3	19.5, 19.8, 19.9	20.5, 21.4, 21.6	19.0, 19.1, 19.3	23.1, 22.9, 22.6	22.5, 22.9, 22.3	21.9, 22.1, 21.5	19.2, 19.6, 18.1	23.4, 23.2, 22.9	23.2, 22.9, 23.0
10 weeks	21.2, 21.2, 21.2	21.2, 21.3, 21.3	20.8, 20.6, 20.9	20.6, 20.8, 20.8	21.0, 20.5, 20.6	22.1, 21.6, 21.7	20.4, 21.0, 20.6	21.5, 21.6, 21.4	36.6, 36.6, 37.0	32.4, 32.6, 32.0
12 weeks	23.0, 22.9, 23.2	21.0, 20.6, 20.7	22.0, 21.2, 21.7	19.4, 18.9, 19.0	23.0, 22.8, 22.5	20.5, 20.3, 20.8	22.9, 22.8, 22.4	20.0, 19.6, 19.3	33.3, 33.0, 33.7	30.0, 29.7, 30.2
14 weeks	20.1, 21.0, 20.8	17.8, 16.0, 15.8	20.1, 20.0, 19.6	17.5, 18.0, 17.9	20.5, 21.2, 21.0	17.5, 17.9, 17.0	22.1, 22.1, 22.0	17.8, 18.0, 18.1	37.0, 37.5, 36.0	25.8, 24.9, 25.0
16 weeks	21.5, 21.5, 21.2	18.5, 19.2, 19.2	20.6, 20.4, 20.0	19.4, 19.6, 19.5	19.6, 20.0, 20.0	20.0, 19.6, 19.2	22.4, 22.6, 22.5	19.2, 19.6, 19.5	32.0, 32.4, 34.0	25.0, 25.2, 25.4
18 weeks	21.8, 22.1, 22.0	22.5, 22.4, 23.0	22.5, 23.0, 22.6	21.6, 21.8, 21.9	21.1, 21.4, 21.5	21.1, 21.4, 21.9	23.4, 23.1, 23.0	22.0, 21.4, 21.9		

Batch No. 200A—Expiration date: June 17, 1941

Interval	Control (freshly prepared each time) H (sec.)	P	Refrigerated (tightly stoppered) H (sec.)	P	Refrigerated (lightly stoppered) H (sec.)	P	Room temperature (tightly stoppered) H (sec.)	P	Room temperature (lightly stoppered) H (sec.)	P
Freshly prepared	19.8, 20.0, 20.2	15.8, 16.2, 16.4	19.8, 20.0, 20.2	15.8, 16.2, 16.4	19.8, 20.4, 19.6	17.0, 17.4, 16.6	19.0, 18.2, 19.2	15.8, 15.6, 15.9	19.4, 19.6, 20.2	16.4, 16.6, 16.8
1 week	20.2, 19.8, 20.8	20.8, 20.6, 20.1	19.2, 20.1, 19.4	21.8, 20.9, 21.0	19.2, 19.6, 19.4	19.8, 20.6, 20.8	19.4, 20.4, 19.5	21.1, 21.4, 21.7	19.2, 19.4, 20.0	20.5, 20.7, 21.2
2 weeks	17.0, 17.2, 17.1	16.9, 17.0, 17.1	17.2, 16.6, 16.0	16.0, 15.2, 16.0	16.2, 16.1, 15.8	16.4, 16.2, 16.5	15.5, 16.0, 16.1	15.5, 16.7, 16.2	16.2, 16.4, 16.1	16.1, 16.4, 16.2
4 weeks	16.8, 16.9, 17.2	17.5, 17.4, 17.8	16.2, 16.4, 16.0	16.2, 15.8, 16.4	16.2, 16.3, 16.5	16.9, 17.2, 17.1	16.4, 16.6, 16.2	17.0, 16.3, 16.2	15.8, 16.0, 16.3	17.1, 17.6, 17.4
6 weeks	18.6, 19.4, 18.8	19.0, 19.1, 19.4	20.1, 20.4, 20.2	18.9, 19.4, 19.5	22.2, 22.0, 22.4	19.0, 19.2, 19.1	19.6, 19.5, 20.2	18.9, 19.4, 19.1	23.1, 22.8, 22.9	19.6, 20.2, 20.3
8 weeks	19.8, 19.9, 19.6	18.9, 19.6, 19.2	20.8, 20.8, 20.5	20.1, 21.2, 21.0	22.9, 22.8, 23.1	22.8, 23.0, 22.7	19.6, 20.4, 20.2	19.6, 19.8, 19.5	22.1, 22.0, 22.4	19.6, 20.0, 19.9
10 weeks	21.6, 21.6, 21.4	21.2, 21.0, 21.6	20.6, 20.8, 21.1	20.4, 20.2, 20.3	21.0, 21.2, 21.3	20.6, 20.5, 20.8	21.0, 21.2, 21.4	20.5, 20.6, 20.3	21.2, 21.4, 21.6	26.5, 27.0, 26.9
12 weeks	21.5, 21.4, 21.0	18.5, 18.8, 19.0	19.6, 20.1, 20.4	19.1, 19.2, 18.8	20.2, 20.5, 20.1	20.0, 20.2, 19.8	20.7, 20.1, 19.9	19.2, 19.0, 19.7	20.6, 20.9, 21.4	28.0, 28.5, 27.7
14 weeks	20.0, 20.0, 20.2	15.5, 15.5, 14.8	20.8, 20.0, 20.2	16.6, 16.1, 17.0	19.6, 20.1, 20.2	19.3, 19.0, 19.0	20.2, 20.8, 21.0	17.5, 17.6, 17.1	22.0, 22.1, 22.1	20.0, 20.1, 20.6
16 weeks	19.8, 20.4, 19.6	18.2, 17.7, 18.0	19.5, 19.8, 20.1	18.5, 18.5, 18.6	19.4, 19.3, 19.1	18.0, 19.0, 18.7	20.4, 20.8, 20.6	18.5, 18.6, 18.6	24.0, 25.2, 24.6	19.5, 20.0, 20.6
18 weeks	20.2, 20.8, 20.5	21.2, 21.7, 21.5	20.8, 21.0, 20.9	17.5, 17.2, 17.2	19.6, 19.9, 20.0	17.0, 17.2, 17.5	20.4, 21.2, 21.0	21.0, 20.8, 21.1	27.3, 28.0, 28.2	

* Supplied as "Stypven" Russell viper venom by Burroughs Wellcome & Co., New York.

parisons could be made between the 2 different batches of venom. Since it was desirable to have blood of as constant composition as possible, the same 2 persons furnished blood for the entire study. By using 2 individuals, 1 served as a control for the other. Both were healthy young adults. However, since even the blood of healthy individuals might vary, venom from freshly opened ampoules served as standards of control at each 2-week period. More than 650 determinations were performed in the course of this study.

Results. The results are given in Table 1. Inspection of the data reveals the importance of control determinations, as periodic fluctuations in the prothrombin times of both subjects were found to occur. In order to correct for these fluctuations the average control values were subtracted from the corresponding average experimental values of each of the 4 stored samples and the results plotted as in Figure 1.
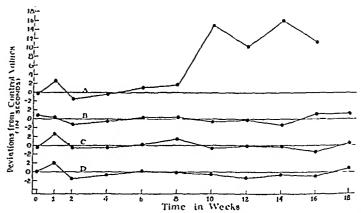
Fig. 1.—Thromboplastic activity of samples of Russell viper venom under different conditions of storage. The differences in prothrombin clotting times between stored samples and the control values are plotted against the duration of storage. Curve A— lightly stoppered, room temperature. Curve B—tightly stoppered, room temperature. Curve C—lightly stoppered, refrigerator temperature. Curve D—tightly stoppered, refrigerator temperature.

It was found that storage at refrigerator temperatures in stoppered or lightly stoppered containers as well as storage in stoppered flasks at room temperature, did not significantly affect the thromboplastic-like activity. The sample which was left lightly stoppered at room temperature showed no change for the first 8 weeks. At this point, however, the activity suddenly decreased very rapidly as indicated by the increased prothrombin time curves. The suddenness and the completeness of the change is surprising, as it would generally be expected that the decomposition would either occur soon after exposure or that it would be a more gradual process.

Summary. 1. Solutions of Russell viper venom maintained their thromboplastic-like activity unimpaired when stored in stoppered or lightly stoppered containers at refrigerator temperature or in stoppered containers at room temperature for the duration of the experiment (126 days).

2. Solutions of Russell viper venom suffered sudden decomposition after about 2 months exposure to the air at room temperature.

3. The prothrombin clotting times of two healthy normal individuals underwent periodic fluctuations over a period of 18 weeks.

REFERENCES

1. Page, R. C., and de Beer, E. J.: J. Lab. and Clin. Med. 28, 912, 1942–43.
2. Page, R. C., de Beer, E. J., and Orr, M. L.: J. Lab. and Clin. Med., 27, 197, 1941–42.
3. Page, R. C., and Russell, H. K.: J. Lab. and Clin. Med., 26, 1366, 1940 41.
4. Quick, A. J.: J. Am. Med. Assn., 110, 1658, 1938.

THE EFFECT OF ARSENIC (FOWLER'S SOLUTION) ON ERYTHROPOIESIS*

A Contribution to the Megaloblast-Normoblast Problem

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Prior to the discovery of liver therapy, arsenic was a common medication in the treatment of pernicious anemia, although no definite benefit from its use could be proved. Minot and Lee[12] believed that the drug acted as a stimulus to the bone marrow, though in larger amounts it appeared to cause destruction of this tissue. Stockman and Charteris[17] studied the action of arsenic on the bone marrow in man and in animals and concluded that there was an increase in the number of "leukoblastic" cells and a marked hyperemia and atrophy of the fat. There were little or no changes in the number or morphologic character of the "erythroblastic" cells. Evans[4] conceived the action of arsenic in pernicious anemia as one of "whipping up" an already overstimulated hemopoietic tissue, thus hastening its final collapse rather than promoting any real progress. It is well known that arsenic and its compounds are destructive to bone marrow as well as a protoplasm poison. Dustin[2] studied the effect of arsenic on the chromatin as it passes through certain phases and noted a nuclear hypersensitivity to the drug (karyoklasia) which occurs as the nucleus approaches a phase of condensation, either chromosomal or prepyknotic.

Tempka and Braun[18] reported the effect of arsenic therapy on a pernicious anemia patient who was observed for a period of 45 days. The patient received daily 150 mg. of arsacetin by mouth and 5 mg. acidum arsenicosum subcutaneously for the first 24 days. The blood findings before treatment were hemoglobin 37%, erythrocytes 1.25 mil., leukocytes 5100 and color index 1.5. Following arsenic therapy there were erythrocytes 3.21 mil., hemoglobin 72%, leukocytes 5900, and color index 1.1. After 17 days of arsenic, the bone marrow showed the

promegaloblasts unchanged, the other forms of megaloblasts somewhat reduced and an increase in the number of pronormoblasts and normoblasts. The pathologic stab neutrophiles were increased. Similar findings were observed in the sternal marrow 45 days after arsenic therapy. Rohr[15] reported the effect of arsenic on the sternal marrow of 2 cases of pernicious anemia. One case who received 1 to 7 mg. acidum arsenicosum daily for 7 days showed an actual decrease in the hemoglobin percentage and in the number of erythrocytes. Sternal marrow aspiration on the 7th day of arsenic therapy revealed marked changes
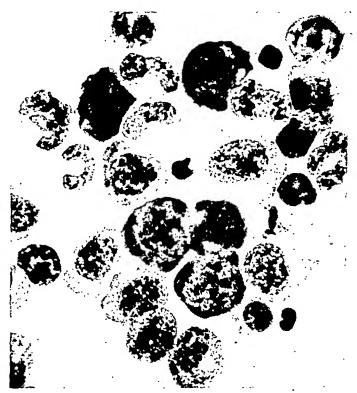
Fig. 1.—Bone marrow, Case 1. Showing megaloblasts and pathologic granulopoiesis. (× 1100.)

in the megaloblastic tissue. Their nuclei were swollen and misshapen and extreme karyorrhexis (karyoclasia) with many bizarre nuclear protuberances and large nuclear bits was a common observation. Arsenic was now discontinued and followed by the intramuscular injection of potent liver extract. The bone marrow examination 11 days later revealed a macronormoblastic regeneration and a disappearance of the pathologic erythropoiesis due to arsenic. Exactly the same changes were observed in a second case. According to Rohr, arsenic brings about a pathologic stimulation of the megaloblasts which consist of a hastening of cytoplasm ripening, nuclear destruction and

nuclear extrusion. This may produce a megalocytic remission in the peripheral blood, but normalization of the pathologic bone marrow never occurs. The effects of arsenic in the other anemias stimulates normal erythropoiesis. On the other hand, Naegeli[13] as late as 1935 maintained that arsenic therapy was capable of producing unquestionable remission in pernicious anemia. Koller[9a] studied the sternal marrow of a pernicious anemia patient who was treated with acidum arsenicosum (10 daily doses—0.002 to 0.010 gm.) and estimated the length of time it takes for basophilic megaloblasts to become megalocytes. Before treatment, the marrow was megaloblastic in type, on the 6th day of arsenic medication, the polychromatophilic megalo-
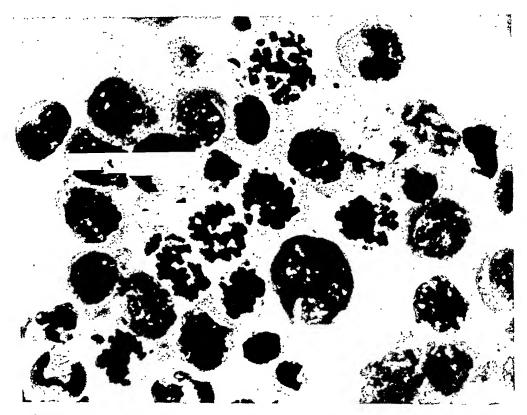
FIG. 2.—Bone marrow, Case 1. After 4 days of arsenic medication. Note the marked karyorrhexis of megaloblasts. (Arsenic sensitive.) (× 1100.)

blasts were more than double in number and on the 10th day orthochromatic megaloblasts were increased approximately 11 times. From these studies he estimated it takes about 10 to 12 days for the maturation of megalocytes in contrast to the 3 to 4 days for normocytes following liver therapy. Koller is aware of the fact that arsenic therapy is unphysiologic.

Ehrlich[3] maintained that the erythroid cells of the primitive prehepatic generation of erythrocytes in the embryo were identical to the megaloblastic generation of red cells characteristic of pernicious anemia during a relapse. He believed in an embryonal reversion of erythropoiesis in pernicious anemia. Recent[7] studies indicate that the red

cells of the primitive generation in the embryo, though morphologically similar, are not identical with the megaloblastic regeneration of pernicious anemia.
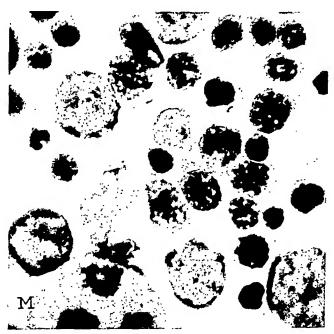
Fig. 3.—Bone marrow, Case 1. Seventy-two hours after 10 cc. of intramuscular liver extract (20 units). Showing conversion to normal erythropoiesis. (Normoblastic.) M. multipolar mitosis. ($\times$ 1100.)
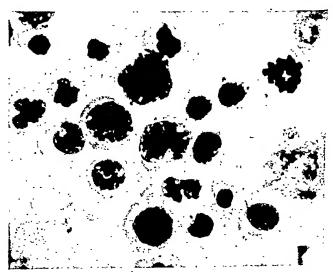
Fig. 4.—Bone marrow, Case 2. After 6 days of arsenic therapy showing maturation of megaloblasts to acidophilic stage. ($\times$ 1100.)

The theory that the megaloblast is a normal erythroid cell which requires the "liver factor" for its maturation to a normoblast has enjoyed a widespread popularity.[1,6,14] On the other hand, the contention that the megaloblast is a pathologic cell and that the hemopoietic principle exerts its action in part by eliminating and inhibiting the formation of megaloblasts is supported by clinical experiments.
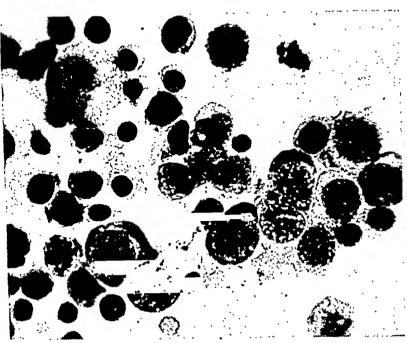
Fig. 5.—Bone marrow from case of sickle-cell anemia. Showing marked erythroid immaturity (pronormoblasts) and normoblasts unaffected by arsenic after 17 days of medication. (Arsenic resistant.) (× 1100.)

Methods. The method used for obtaining and studying bone marrow has been described in detail elsewhere.[10] To state it briefly—1 cm. of sternal marrow is aspirated through a dry modified 16-gauge needle into a dry syringe and placed immediately into a paraffin-lined tube containing a small amount of powdered heparin, an anticoagulant; the marrow material is transferred to a Wintrobe hematocrit tube; centrifuged 5 minutes at about 2000 r.p.m.; the layers into which the marrow separates (erythrocytes, bone marrow cells, plasma, and red and yellow fat) are recorded; the bone marrow cell layer is mixed with an equal volume of plasma in a paraffin chamber; and films of this mixture are made, stained with May-Grunwald-Giemsa dyes, and studied microscopically for cell distribution and types.

Studies of the peripheral blood drawn just prior to the sternal aspiration are made in all cases. This includes counts of erythrocytes, leukocytes and platelets; hemoglobin and hematocrit determinations, mean corpuscular volume, hemoglobin and hemoglobin percentage; sedimentation rate, icteric index, reticulocyte count and differential leukocyte counts.

Arsenic in the form of Fowler's solution (Liquor Potassii arsenitis corresponding to 1% AS_2O_3 was administered in milk, beginning with 4 minims 3 times a day and increasing the dosage 3 minims each successive day until the dosage of 15 minims 3 times a day was reached, or until toxic symptoms of the drug were manifested. Some of these are hyperesthesia of the oral mucous membrane, sensation of esophageal irritation, severe gastro-intestinal disturbances such as anorexia, cardialgia, nausea, vomiting and diarrhea, puffiness of the eyelids and skin rashes. The drug was then discontinued or

the dosage was gradually decreased. The toxic effects of arsenic were observed in all cases of pernicious anemia, in some instances as early as the 3d day following medication.

Seven cases of pernicious anemia were studied before treatment after the administration of arsenic and following intramuscular liver injections. Table 1 shows that those cases with a severe anemia and marked megaloblastic hyperplasia of the bone marrow are extremely sensitive to arsenic. Although there was no improvement in the anemia, a reticulocytosis as high as 31% was observed in the peripheral blood. The bone marrow, as early as the 4th day, revealed marked toxic and destructive changes in the megaloblastic tissue consisting of various phases of karyorrhexis such as swollen and misshapen nuclei, bizarre nuclear protuberances, nuclear fragments, nuclear destruction and nuclear extrusion. Mitotic figures were infrequent. There was a definite and pronounced maturation of megaloblast to the acidophilic stage. There were no morphologic indications that megaloblasts matured to normoblasts.

In pernicious anemia marrow after arsenic treatment the pronormoblasts and later stage cells are intact and they may even be adjacent to disintegrating megaloblasts. Following intramuscular liver therapy there is a tremendous proliferation of normoblasts in as short a period as 24 hours. This is followed by a gradual improvement in the anemia in the peripheral blood. Obviously the arsenic-sensitive pathologic megaloblastic tissue which is in a karyorrhectic condition cannot take part in the normoblastic transformation and normalization of the bone marrow in pernicious anemia following liver treatment.

Arsenic was administered to normal controls, cases of cirrhosis of the liver, sickle-cell anemia, erythroblastosis, polycythemia vera, chronic myeloid leukemia, carcinoma of the stomach and chronic hemorrhagic anemia (Table 2). In these various clinical disorders in which the bone marrow consists of a moderate to marked erythroid hyperplasia and immaturity no significant degenerative changes of the erythropoietic tissue were observed. In spherocytic jaundice and refractory anemia with a macrocytosis following the administration of arsenic, karyorrhexis in the polychromatophilic and acidophilic normoblasts in the bone marrow was a conspicuous feature. In none of the bone marrows were the pronormoblasts affected by arsenic. These findings are additional evidence for the separation of the pathologic megaloblastic series from the normoblastic series of erythrocyte regeneration.

Jones,[8] in a comprehensive article has discussed in detail the morphologic, physiologic, chemical and biologic distinction of megaloblasts. This investigator believes the morphologic aspects of erythropoiesis have been unduly neglected and have resulted in calling all immature erythroid elements, "megaloblasts," whether they are seen in normal bone marrow, in that of various clinical conditions, or in bone marrow of certain laboratory animals.

In my own study of 2325 sternal marrows, megaloblasts were observed almost entirely in patients with anemias due to a deficiency

TABLE 1.—CASES OF PERNICIOUS ANEMIA TREATED WITH ARSENIC AND LIVER

	Before Treatment						
Case No.	1	2	3	4	5	6	7
Erythrocytes, millions	1.14	1.30	1.47	2.34	2.46	2.60	2.90
M.C. volume, C.M.	140	145	122	130	138	120	121
Reticulocytes, %	1.0	0.5	0.5	0.5	0.1	0.5	0.5
Bone marrow, type	Megaloblast	Megaloblast	Megaloblast	Megaloblast and normoblast	Megaloblast and normoblast	Megaloblast and normoblast	Megaloblast and normoblast
	After Arsenic						
Days on arsenic	4	6	8	14	6	7	8
Erythrocytes, millions	1.40	1.20	1.63	2.90	2.39	2.50	2.80
Reticulocytes, %	19.0	31.0	18.0	12.0	8.0	3.5	5.0
Bone marrow (karyorrhexis, %)	90.0	88.0	72.0	86.0	42.0	59.0	65.0
	After Liver						
Days after liver	2	3	13	⋯	3 mos.	2 mos.	16 days
Erythrocytes, millions	1.20	1.17	2.34	⋯	4.70	4.30	3.80
Reticulocytes, %	22.0	37.0	6.0	⋯	0.5	0.5	1.0
Bone marrow (type)	Normoblast and some karyorrhexis	Normoblast	Myeloid and normoblast	⋯	Normal	Normal	Myeloid and normoblast

TABLE 2.—VARIOUS CLINICAL DISORDERS TREATED WITH ARSENIC

Blood disorder	Before				Days on arsenic	Following arsenic			
	Hemoglobin (gm.)	Erythrocytes (mill.)	Reticulocytes (%)	Bone marrow (type)		Hemoglobin (gm.)	Erythrocytes (mill.)	Reticulocytes (%)	Erythroid cells affected (karyorrhexis)
Normal controls (4)					8–18	13.0	4.64	0.6	None
Cirrhosis of liver (macrocytic)	12.0	3.20	0.5	Pronormoblast, normoblast	10	10.8	2.90	0.5	Normoblast (slight)
Refractory anemia (macrocytic)	7.4	1.86	0.5	Normoblast	21	7.4	2.25	6.0	Normoblast (marked)
Sickle-cell anemia (macrocytic, 2)	9.5	2.95	20.0	Pronormoblast, normoblast	10–17	9.5	2.68	12.0	None
Erythroblastosis (macrocytic, 2)	10.0	2.26	40.0	Pronormoblast	16	6.5	1.61	5.0	Normoblast (mod.)
Spherocytic jaundice (macrocytic)	7.9	2.78	20.0	Normoblast	11–15	8.0	2.77	25.0	Normoblast (marked)
Polycythemia vera (normocytic, 2)	19.0	7.79	1.0	Pronormoblast, normoblast	(Venesection)	15.5	5.64	1.5	Normoblast (mod.)
Chronic myeloid leukemia (normocytic)	8.5	2.90	1.0	Pronormoblast, normoblast	30	8.25	3.30	4.5	Normoblast (slight)
Ca. of stomach (microcytic)	4.5	2.61	1.0	Normoblast	14	4.5	2.50	1.5	None
Chronic hemorrhage (microcytic, 2)	5.0	3.01	0.5	Pronormoblast, normoblast	13–17	4.4	3.35	1.0	Normoblast (slight)

of liver principle. Rohr[16] has had a similar experience in a series of more than 1800 sternal marrow examinations.

In pernicious anemia, liver extract and arsenic affect the bone marrow differently. The physiologic effect of liver extract results in the conversion or transformation of a megaloblastic marrow to a normoblastic one in 24 to 72 hours. The pathologic effect of arsenic causes no delay in the conversion or transformation to a normoblastic marrow following intramuscular liver treatment. The pathologic cell of the granulocytic series and the megakaryocytes are unaffected by arsenic. Following liver therapy the abnormal granulopoietic tissue and the megakaryopenia gradually returns to normal. It is interesting to note that arsenic does not affect the pronormoblasts seen in various clinical conditions presenting marked erythroid hyperplasia and immaturity.

The implications are great that the effect of liver extract is one of eliminating the pathologic megaloblasts and suppressing their further multiplication.[5]

The resultant reticulocytosis following arsenic therapy is due to the maturation of megaloblasts to reticulated megalocytes, since there is no morphologic indication that megaloblasts are maturing to normal reticulocytes. Normally following liver therapy in pernicious anemia, megaloblasts complete their maturation as reticulated and mature megalocytes. The resultant reticulocytosis is composed of reticulated megalocytes and normal reticulocytes. According to Jones[9] this not only indicates the reëstablishment of normal erythropoiesis, but also that the marrow is being purged of its pathologic red cell series, the megaloblasts.

It is unfortunate that blood cells under embryonic, normal adult and pathologic conditions all have their nuclei pass through a pyknotic stage before becoming a reticulocyte. Hence "tagging" the megaloblasts with arsenic makes it easier to trace cellular maturation which were followed with difficulty after liver extract alone.

The mechanism by which a megaloblastic marrow is rapidly transformed or converted into a normoblastic one is an unsettled question. Normal bipolar mitosis does not explain the rapid and dramatic conversion. Koller[9a] has suggested that young multinucleated megaloblast cells may subdivide and heteroplastically form a quantity of normoblasts. Since the arsenic-sensitive megaloblasts are not transformed into normoblasts, the finding of multipolar mitoses and multinucleated erythroid[5,11] cells which are frequently seen in pernicious anemia marrows may play a rôle in the rapid conversion to a normoblastic type.

The effect of arsenic on the normoblasts in spherocytic jaundice is probably the result of the fundamentally abnormal type of erythropoiesis which produced the spheroidocytes. The toxic action of the drug on the erythroid cells in the case of refractory anemia cannot be satisfactorily explained.

Conclusions. 1. The megaloblasts in the bone marrow of patients with pernicious anemia during relapse are arsenic sensitive and the pronormoblasts as seen in normal bone marrow and in the bone marrow of most cases of anemias with an erythroid immaturity are arsenic resistant.

2. The "liver principle" can exert its physiologic effect on the bone marrow in pernicious anemia in the presence of a karyorrhectic megaloblastic tissue which presumably is in a poorly functional condition due to the toxic effect of arsenic.

3. The action of the hemopoietic principle is probably to effect the elimination (maturation) and suppression of the megaloblasts in the bone marrow. It is not clear as to how liver extract effects a stimulation of the normoblastic tissue. It is clear that arsenic has no such effect.

4. The arsenic serves as a convenient agent to separate the pathologic reticulocytes originating from the megaloblasts from those derived from normoblasts. When the latter appear, the anemia is corrected.

It is especially important for the reader to keep evidence separate from deduction in this article. The interesting observations might perhaps be brought into line with other views as to the rôle of the megaloblast in erythrypoiesis.—Editor.

REFERENCES

1. Doan, C. A., Cunningham, R. S., and Sabin, F. R.:   Contrib. Embryol., 16, 163, Pub. No. 361, Carnegie Inst., Washington, 1925.
2. Dustin, A. P.:   Strasbourg Med., 85, 12, 1927.
3. Ehrlich, P.:   Verhandl. d. gesellsch. d. Charite-Aerzte, 1880.
4. Evans, F. A.:   Pernicious Anemia, Baltimore, Williams & Wilkins Co., 1926.
5. Fieschi, A.:   Semeiologia del Midollo osseo: Studio di Morfologia Clinica in Ferrata, A.: Biblioteca "Hæmatologica," Pavia, Tipografa Già Cooperativa, vol. 6, 1938.
6. Isaacs, R.:   The Erythrocytes, in Downey, Hal: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1, 5, 1938.
7. Jones, O. P.:   Downey's Handbook of Hematology, New York, Paul B. Hoeber, Inc., 3, 2045, 1938.
8. Jones, O. P.:   Arch. Path. 35, 752, 1943.
9. Jones, O. P.:   Proc. Soc. Exp. Biol. and Med., 38, 222, 1938.
9a. Koller, F.:   Deutsch. Arch. f. klin. Med., 184, 567, 1939.
10. Limarzi, L. R.:   Illinois Med. J., 75, 38, 1939.
11. Limarzi, L. R., Levinson, S. A., and Jones, R. M.:   J. Am. Med. Assn., 118, 1004, 1942.
12. Minot, G. R., and Lee, R. K.:   Boston Med. and Surg. J., 177, 761, 1917.
13. Naegeli, O.:   Wien. klin. Wchnschr., 48, 225, 1935.
14. Osgood, E. E., and Ashworth, C. M.:   Atlas of Hematology, San Francisco, J. W. Stacy, Inc., 1937.
15. Rohr, K.:   Das menschliche Knochenmark, Leipzig, Georg Thieme, 1940.
16. Rohr, K.:   Knochenmarksmorphologie des menschlichen Sternal punktats, Berlin, Urban & Schwarzenberg, 1937.
17. Stockman, R., and Charteris, F. J.:   J. Path. and Bacteriol., 8, 443, 1903.
18. Tempka, T., and Braun, B.:   Folia hæmatol., 48, 355, 1932.

A STUDY OF HEMOGLOBIN METABOLISM AND HEMATOLOGY IN A CASE OF CONGENITAL HEMOLYTIC JAUNDICE DURING (A) CLINICAL CRISIS, (B) REPEATED TRANSFUSIONS, AND (C) BEFORE AND AFTER SPLENECTOMY

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This case is reported because of the continuous period of study before splenectomy, through the course of a clinical crisis with evidence of liver dysfunction, during repeated blood transfusions, and

finally, after splenectomy. Similar studies of hemolytic jaundice before and after splenectomy have appeared in the literature[7,8,17] but none covers all these various phases.

There are several reports of clinical or pathologic evidence of liver complications occurring during the course of hemolytic jaundice of various types.[3,15,19] The clinical picture includes: (1) liver enlargement; (2) repeated attacks of nausea, vomiting, fever, and progressive jaundice, with upper right quadrant pain in the presence or absence of gall stones; (3) a direct van den Bergh reaction in the serum, or one changing from indirect to direct during the acute episode. The pathologic changes observed include: (1) marked enlargement of the liver with no histologic reports; (2) a perilobular congestion of characteristic type; (3) some degree of parenchymal degeneration, varying from mild with recovery to severe with terminal acute yellow atrophy.[2,3,4] The case reported by Farrar[3] showed moderate liver degeneration with recovery following splenectomy. The clinical condition was aggravated by transfusions. They suggest that an acute liver failure is one of the pathogenic mechanisms of the clinical crises observed in hemolytic anemia.

The effect of transfusions on the course of blood destruction in sickle cell anemia and in congenital hemolytic jaundice has been extensively studied by Josephs.[9] He observed inhibition of the hemolytic process with whole blood and plasma transfusions,[8] as well as with pig plasma.[17] Others have noted the dramatic results from transfusions in the so-called Lederer's acute hemolytic anemia.[1,11] Transfusions were long used as the mainstay in management of acute phases of congenital hemolytic anemia also,[5,13] but more recently warnings have been published against their use, as liable to aggravate the condition and even prove fatal.[3,10,14]

There is adequate evidence in the literature for the value of splenectomy in congenital hemolytic anemia. However, recent publications[4,6,10] indicate that under certain circumstances splenectomy may be of no value in this condition, and the patients die. Some of these show a specific type of liver change characterized by perilobular congestion.

Case Report. J. H., white male, 15 years of age, was admitted to Charity Hospital of New Orleans (L. S. U. Med. Serv.) 12-10-40, complaining of anorexia, URQ pain, fever, jaundice, and enlarged spleen. He had apparently had no complaints up to 2 months previously, when he began having chilly sensations followed by malaise and anorexia. Later it was noticed he had fever and jaundice. He was nauseated and vomited several times. No abnormality was noted about the bowel action or the stools. The fever and vomiting continued and pain in the upper right abdomen occurred. He became delirious in a few days. His condition was thought to be due to gall bladder disease, and he was taken to a private hospital. On admission, the family stated that he had a very low red blood count. He continued to have high fever and the enlargement of the spleen was noted at this time. He stopped vomiting and regained his appetite, but continued to have fever. Following 5 blood transfusions over the course of his 19-day stay in that hospital he improved sufficiently to return home. He remained at home until the present admission, feeling well and gaining strength up to 1 week ago, at which time

he again began to have fever, lose his appetite and feel nauseated. He also began to have pain and soreness in the upper right quadrant of the abdomen. His past history was irrelevant except that he had had a chronic ulcer of the middle third of the left leg several years previously which resisted treatment, but finally healed after a period of 3 months.

His family history was significant in that one brother had had an attack similar to that of the patient's after acting as a donor for him on his previous hospitalization. This brother was examined and found to have a large spleen, and has since been operated on. At the same time, the father was noted to have slightly icteric scleræ, and examination revealed a moderately enlarged spleen. His red blood cell fragility was increased, 0.6 to 0.38 (control 0.42 to 0.32).

Physical Examination. The temperature was 103.4° F., pulse 130, respiration 24, blood pressure 120/68. He was normally developed, but quite emaciated. His skin was hot, dry, and slightly jaundiced. The scleræ were definitely jaundiced. Lungs were clear, and heart negative except for the tachycardia and a systolic murmur at the apex. The abdomen was flat with a bulge in the left flank. Here a firm, notched, tender mass with rounded borders was felt, and thought to be the spleen. The liver was palpable 2 fingers below the costal margin on deep inspiration and was quite tender. On the left leg, one-third of the way from the ankle on the anterior surface was a pigmented scar measuring 5 x 3 cm.

Laboratory Reports. RBC, 2.72 million; MCV, 83μ^3; MCH, 32$\gamma\gamma$; RBC fragility, 0.6 to 0.34; control, 0.42 to 0.32. About 10% spherocytes were present. White blood cells, 11,200; neutrophils, 60; lymphocytes, 40%. Blood Type II. Urine amber, acid, sp. gr. 1.030, alb. 0, sugar 0, bile 0; microscopic: occasional hyaline and fine granular casts, and occasional white blood cells. Icterus index, 18 units. Blood Kolmer and Kline, negative. Roentgen ray of lungs and heart, negative. Gall bladder spot plates showed multiple stones in region of gall bladder and cystic duct.

Clinical Course. 12-13-40, transfusion 500 cc. cross matched blood, type unknown. 12-16-40, much improved, temperature normal. 12-20-40, ambulatory. 12-21-40, fever 100.2° F., jaundice increasing, complaining of pain in RUQ. Thought to be having a mild crisis. 12-24-40, intravenous hippuric acid liver function test, 0.59 gm. (the intravenous injection of sodium benzoate was immediately followed by nausea, vomiting, and urticaria which subsided immediately following 5 min. of epinephrine intramuscularly).

Transfusions were given: 1-7, 300 cc. Type IV; 1-12, 350 cc. Type II; 1-18, 350 cc. Type II.

The stercobilin and urobilin excretions were measured from 12-16 onwards and are illustrated in the accompanying chart. Following the initial rise of the RBC level, because of the increasing blood destruction as evidenced by the pigment excretion, and the ultimate fall of RBC, reticulocytes, and hemoglobin, coupled with progressive enlargement of the spleen which became more tender, it was felt that further management of this type was not indicated, and that surgery was necessary. Splenectomy was carried out by Dr. J. D. Rives of the L. S. U. Surgery Department on 2-10. It was noted at operation that besides the large spleen there were 10 or 12 small accessory spleens in the hilar region. All of them were removed. Immediately following splenectomy, 900 cc. of cross matched blood were given. That afternoon the RBC level was 4.45 million. The immediate postoperative course was marked by a sharp rise of temperature which subsided rapidly. The van den Bergh reaction was direct. The laboratory data are shown in the accompanying chart. (Fig. 1.)

The spleen weighed 1150 gm. and had 4 infarcts, 3 old ones and 1 more recent.

Discussion. The crises of hemolytic jaundice may be characterized by the prominence of various features. Gripwall[6] describes them as (1) thermic; (2) abdominal; (3) essential blood crises. The mechan-

ism of the so-called thermic crises, if they exist divorced from other phenomena, is not clear. His description of the abdominal crises fits those observed by ourselves and others, and which we feel, in agreement with Farrar, to be associated with changes in liver function and structure and not necessarily with increased blood destruction. Further study is necessary in those instances simulating appendicitis as happens in sickle cell anemia. The essential blood crises are the hemoclastic type producing severe, even fatal anemia. It is possible that
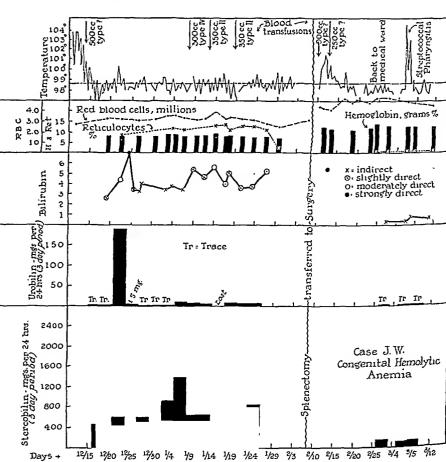
FIG. 1.—Laboratory data on case of congenital hemolytic jaundice.

these various clinical pictures are delineated by predominant manifestations of essentially the same mechanism. Not enough is known about the detailed pathologic physiology of the disease to make any definite statement as to the nature of this mechanism.

When this patient was first seen he presented a picture of hepatitis with splenomegaly. The history and examination of the father who was at the bedside immediately suggested congenital hemolytic jaundice in crisis. This occurrence of hepatitis in hemolytic anemia has

not been sufficiently studied. (The term "hepatitis" is used to describe the clinical picture. We have no data on the actual pathologic anatomy.) We have repeatedly observed it in sickle cell anemia. Frequently the patient is immediately given a transfusion, as was done in this instance, but that spontaneous recovery[5] from the episode does occur is also obvious from the second such attack observed in this case. Josephs calls attention to the possibility of confusing spontaneous variation with the apparent therapeutic effect of a transfusion.[7] Gairdner[5] claimed that recovery was more rapid following transfusion than without.

During the second crisis in this patient we were able to study the pigment metabolism and liver function. The marked sudden increase of urinary urobilin, rapid increase of bilirubinemia with change of the van den Bergh from indirect, through slight to moderate to strong direct type, the enlargement and tenderness of the liver, and the diminished hippuric acid synthesis as measured by the Quick intravenous test suggested diminished liver function. These findings then rapidly cleared with no therapeutic attempts. It can be seen from the pigment and hematologic studies that there was no marked increase of blood destruction associated with this series of events.

The study of hemoglobin metabolism in various blood dyscrasias has been given great stimulus by Watson's studies.[17,18] He reviews the question of the relationship of urobilinogen excretion to blood destruction and liver function, and concludes that alterations of blood destruction influence fecal excretion, but that change in liver function is the most important factor affecting urobilinogen excretion in the urine.

In our patient, there then followed a progressive rise of blood destruction of only moderate degree as measured by pigment excretion. Transfusions were begun to study their effect in inhibiting the hemolytic process. As can be seen from the chart, a preliminary decrease in blood destruction followed small transfusions (300 to 350 cc.) first of Type IV and then Type II. Following this a very marked increase in pigment excretion and a progressive drop in red blood cells, hemoglobin, and reticulocytes occurred. During the course of transfusions, the patient was continuously febrile. The spleen became progressively larger, the liver was tender and enlarged. The van den Bergh was slightly to moderately direct in type and there was continuous excretion of urobilin above the normal amounts (0 to 4 mg. normal). There was not the degree of alteration that was seen during the acute crisis from December 20 to 25, but qualitatively the changes were similar and appeared to differ only in degree. It appears that the retention of bilirubin in the body at this time might account for the apparent decrease of pigment excretion in the stools, but subsequently there was a marked increase of pigment in the stools and definite inhibition of blood regeneration. It is possible that sequestering and destruction of the transfused erythrocytes by the spleen and the infarctions accounted for the marked increase in the splenomegaly and of pigment excretion noted. Certainly the 1000 cc. of blood given over a

period of 12 days had little effect on the red blood cells and hemoglobin level of the peripheral blood. Suppression of bone marrow function is likewise evident from the drop in red blood cells, hemoglobin and reticulocytes.

Following splenectomy and massive transfusion, the red blood cells and hemoglobin remained at near normal levels. There was a sharp febrile reaction postoperatively and the plasma bilirubin was found elevated and showing a strong direct reaction. Meulengracht[12] has mentioned this sharp rise of temperature that occurs after splenectomy in many such patients, and Eppinger[16] has called attention to the change in the van den Bergh, which he ascribes to liver damage due to anesthesia. Possibly the livers of these patients are more susceptible to such nocuous influences as anesthetics of certain types.

The tenderness and enlargement of the liver disappeared rapidly and have not recurred in the year since splenectomy. The studies subsequent to splenectomy are illustrated in the chart.

Summary. 1. A case of congenital hemolytic jaundice is presented in which hematologic and pigment studies were carried out through the course of a crisis, repeated transfusions, and after splenectomy.

2. During the crisis certain observations indicated decrease of liver function which cleared spontaneously. There was no evidence of marked blood destruction. These changes have been observed also in certain crises of sickle cell anemia. The findings suggest the theory that liver disease may be a factor in the crises of such cases.

3. Transfusions were followed by a progressive enlargement of the spleen. There then occurred a marked increase in blood destruction, drop of red blood cells, hemoglobin, and reticulocytes. It is probable that the transfused red cells were sequestered in the spleen and rapidly destroyed, leading to the marked stercobilin excretion.

4. Splenectomy was followed by a return to normal in the red blood cells, hemoglobin, reticulocytes, bilirubinemia, and pigment excretion. All clinical symptoms and signs disappeared.

REFERENCES

1. DAMESHEK, W., and SCHWARTZ, S. O.: Medicine, **19**, 231, 1940.
2. DAWSON, L.: Brit. Med. J., 1, 921, 1931.
3. FARRAR, G. E., BURNETT, W. E., and STEIGMAN, A. J.: AM. J. MED. SCI., **200**, 164, 1940.
4. FREUND, M.: Am. J. Dis. Child., 43, 643, 1932.
5. GAIRDNER, D.: Arch. Dis. Child., 14, 109, 1939.
6. GRIPWALL, E.: Acta med. Scandin., Suppl., **96**, 1, 1938.
7. JOSEPHS, H. W.: Bull. Johns Hopkins Hosp., 62, 53, 1938.
8. JOSEPHS, H. W.: Bull. Johns Hopkins Hosp., 62, 70, 1938.
9. JOSEPHS, H. W.: Bull. Johns Hopkins Hosp., 62, 25, 1938.
10. LAWRENCE, J. S.: Internat. Clin., 2, 221, 1937.
11. LEDERER, M.: AM. J. MED. SCI., 179, 228, 1930.
12. MEULENGRACHT, E.: Handbook of Hæmatology, H. Downey, New York, Paul B. Hoeber, 3, 2446, 1938.
13. MURRAY-LYON, R. M.: Brit. Med. J., 1, 50, 1935.
14. SHARPE, J. C., and DAVIS, H. H.: J. Am. Med. Assn., 110, 2053, 1938.
15. TILESTON, W.: Medicine, 1, 355, 1922.
16. VARELA-FUENTES, B., and CAZANI, R. (quoted by): Le Sang, 13, 912, 1939.
17. WATSON, C. J.: Arch. Int. Med., 59, 206, 1937.
18. WATSON, C. J.: Handbook of Hæmatology, H. Downey, New York, Paul B. Hoeber, 4, 2446, 1938.
19. WISE, W. D.: Am. J. Surg., 20, 722, 1933.

THE HEART SIZE AND PULMONARY FINDINGS DURING ACUTE CORONARY THROMBOSIS

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Discussion in the literature of the incidence of cardiac enlargement and the degree of pulmonary congestion during and following coronary thrombosis has been based chiefly on the weight of the heart and the lung findings at necropsy. A few studies have been made of the effect of coronary thrombosis on the size of the heart as determined by Roentgen rays. But the infrequency of the Roentgen ray films taken in the various series have not permitted definite conclusion as to the presence or absence of cardiac enlargement in the days immediately following the coronary accident. A few case reports have been published concerning the development of left ventricular aneurysm following myocardial infarction.[3,7] Horine and Weiss[4] reported that 20 patients who had normal sized hearts at the time they experienced a coronary thrombosis did not develop roentgenologic evidence of cardiac enlargement although they were observed subsequently from 5 months to $9\frac{1}{2}$ years. However, they reported only initial and final Roentgen rays, although in some cases *interim* Roentgen ray examinations were also made. Palmer,[5] in a study of the size of the heart after coronary thrombosis, found no example of acute dilatation of the heart in 27 patients examined within a month of the attack. He did find enlargement of the heart by Roentgen ray in 64% of 200 patients who had survived an attack of coronary thrombosis. About one-third of the patients failed to show or to develop enlargement though watched over periods averaging more than 3 years following the first attack of coronary thrombosis. Other authors[1,6] have expressed somewhat different opinions regarding size of the heart following coronary thrombosis. White[8] states that the enlargement, chiefly of dilatation of the left ventricle, may come on rapidly with cardiac infarction. Fishberg[2] states that the heart is not enlarged above the dimensions present prior to the occlusion. However, no report has been made in which a series of successive Roentgen rays of the heart were taken to discern the change in cardiac size which might occur in the days or weeks following the myocardial infarction.

Method of Study. The method of teleoroentgenography was used to determine the heart size and shape in the patients in this study. The Roentgen rays were taken with the patient in a sitting position. Great care was exercised in the handling of these patients because of the gravity of their cardiac condition. No untoward occurrences were encountered in any of the patients as a result of this study. The patients were permitted to sit up on the edge

of the bed without any active movement on their part, being given every necessary support by 2 individuals during the entire procedure. The Roentgen ray tube was placed 5 feet away from the patient and the film holder was kept in contact with the anterior surface of the chest. The Roentgen ray was taken during a phase of quiet respiration since marked changes can be produced in the size and shape of the heart by the diaphragmatic movements accompanying forced inspiration or expiration. The sitting position was chosen since the heart size may be increased in the recumbent position because of an increased return of blood to the heart in that position resulting in a physiologic dilatation.[9] Likewise the heart shadow may be decreased in the standing posture due to decrease in the return of blood to the heart. Furthermore, distortion of the heart size and shape by undue elevation of the diaphragm is less likely in the sitting than in the recumbent positions. In addition, standing would of course be contraindicated by the presence of a myocardial infarction.

The chief difficulty in the application of roentgenology lies, not in the technique, but in the interpretation of the normal limits of heart size, shape, and action, and, therefore, in the diagnosis of slight abnormalities. There are so many factors (e. g., age, sex, habitus, respiration) resulting in individual variations within the normal range, that it is at present impossible to recognize them all, or to take them all into consideration in the evaluation of size or shape. Furthermore, important changes may occur in heart size or shape insufficient to produce definite roentgenologic abnormalities at the time of examination, but which would have been noted if comparative studies had been previously made. Obviously successive records of heart size and shape in the same individual carefully made should be more useful than a single comparison with a table of normal averages. It is, however, often impossible to possess any information about the Roentgen ray findings prior to the onset of trouble in a given patient. Certain measurements of heart size are in routine use and are of value. The one employed in this investigation is the cardiothoracic ratio which is the ratio of the transverse diameter of the heart shadow to the internal diameter of the chest. Although it admittedly is only fairly reliable as an index of cardiac enlargement, it is a simple and useful measure of heart size.

This study was made on 16 patients. Each had had attacks of undoubted acute myocardial infarction 12 to 60 hours prior to entering the Peter Bent Brigham Hospital. As soon after entry as possible (in the majority of cases within 24 hours of the acute episode) the initial Roentgen ray was taken in the manner already described. Subsequent Roentgen rays were taken with few unavoidable exceptions (2 patients died during the 2d week of hospitalization and contact with 2 patients was lost after the 3d and 4th months respectively) on the 3d, 5th, 12th and 28th days following admittance to the hospital and then at the end of the 3d and 6th months after the coronary accident. Figure 1 illustrates the successive Roentgen ray films of Case 13. In addition all but 3 of the patients had a roentgenkymogram taken usually on the 28th day of hospitalization. A total of 113 Roentgen rays was studied for this report. Furthermore, the patients were all followed carefully clinically with frequent examinations, electrocardiograms, blood pressure readings, blood counts and other pertinent data. The period of observation over which the patients were seen varied from 1 week to 7 months with an average for the entire group of 4.7 months. If the 2 deaths at the end of the first week were omitted, the observation ranged from 3 to 7 months with an average of 5.3 months.

The necessary measurements were determined from each Roentgen ray and the cardiothoracic ratio calculated. It was decided that a total change of less than 1 cm. in the transverse diameter of the heart could be considered to be within the limit of Roentgen ray error in this study, considering the difficulty in the technique in these very ill patients and the physiologic changes in heart size occurring among other things with the systolic and diastolic movements of the heart. It is true, however, that a change of less than 1 cm. when accompanied by a change of shape may have considerable significance, but a distinct change in shape did not occur in this series. In order to determine the presence of a significant change in the heart size in the successive Roentgen

rays of any one individual, the difference in the successive cardiothoracic ratios of each patient was calculated and then it was determined whether these differences were equivalent to a change in the transverse diameter of 1 cm. or more. Since Roentgen rays prior to the coronary occlusion were not available, the size of the heart on the successive Roentgen rays was referred to that on the first film. Special attention was paid to the appearance of the lung fields in the successive Roentgen rays to provide information upon the extent of pulmonary congestion in patients with acute coronary occlusion.

Results. The 16 patients studied present a number of clinical features, some of which will be analyzed in this report. Ten of the patients had had previous attacks of angina pectoris over periods varying from 3 weeks to 2 years, while 6 had no previous episodes of precordial or analogous pain. As is usually the case in this condition there was a great predominance of males, the ratio being 12 men to 4 women. The location of the lesion in the heart could be determined fairly accurately from the electrocardiogram since the electrocardiographic changes were quite marked in all the cases. Of the 16 cases, 12 had anterior myocardial infarctions and in the remainder the lesion was situated in the posterior wall of the heart. The blood pressures of 7 patients were moderately elevated during the first few days of hospitalization but all except 2 of these subsequently fell to more normal range. Of the entire series, 8 presented enlarged hearts initially, 5 were in the upper limits of normal and 3 were definitely normal. Six of the roentgenkymograms showed diminution or decrease of the normal pulsations along the left border, near the apex. The other 7 showed no abnormal change. Five complications occurred in the entire series. Two patients died from bronchopneumonia and perforation of the myocardium respectively; the other three complications included an attack of lobar pneumonia, phlebitis of the right and left lower extremities with pulmonary infarction, and a right hemiplegia subsequent to cerebral embolism. These 3 patients eventually recovered.

The lung findings in the Roentgen rays were sufficiently noteworthy to attract special attention. Only in 4 of the patients were the pulmonary fields essentially clear. The remainder showed either a fine or coarse diffuse mottling usually in the lower half of the lung fields and the hilar regions, or definite cloudiness in one or both of the lung bases. The pulmonary congestion, as a rule, was maximum in the first week and tended to decrease or disappear in the second week. The Roentgen ray photographs of Figure 2 demonstrate the initial evidence of pulmonary congestion and the subsequent clearing of the lungs during the first 2 weeks following the coronary accident. Auscultation of the lungs during the first week of hospitalization revealed the presence of basal râles in only 7 patients in spite of the fact that 12 of them showed roentgenologic evidence of pulmonary congestion. In the remaining 4 patients evidence of pulmonary involvement was lacking on both Roentgen ray and physical examination. It was found necessary to give digitalis to 3 patients who had somewhat more evidence of cardiac decompensation than the basal râles usually found in patients with coronary thrombosis. One of these patients had taken the drug before

the coronary occlusion and the other 2 required it on the 7th day following the accident because of increasing signs of cardiac failure.
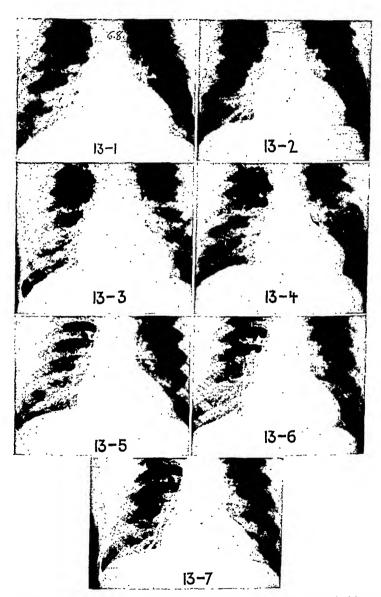
FIG. 1.—Seven successive Roentgen ray films of Case 13 taken over a period of 6 months following the coronary accident.

Eight patients showed no significant change in heart size in any of their films, while 8 others did show a significant increase or decrease in one or more of their Roentgen rays following the coronary occlusion. Table 1 shows the details of the changes in all the Roentgen rays of the series. Table 2 summarizes only those Roentgen rays which showed

a significant change (increase or decrease of 1 cm. or more) in the transverse cardiac diameter. In all the calculations, measurements taken on subsequent films were referred to those of the initial Roentgen ray which was used thus in the manner of a base line. The question arises as to what change, if any, occurred during the time elapsing between the onset of the cardiac accident and the time the first Roentgen ray was taken, but the data of this study do not give any information on this subject. It is noteworthy that 4 of the 8 patients included in Table 2 showed a significant change in only an isolated Roentgen ray and in 3 it was a decrease and in the other an increase. In con-
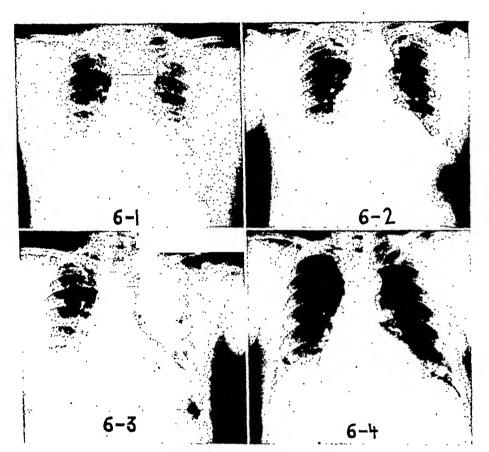
FIG. 2.—Roentgen ray films of Case 6 taken during the first 2 weeks following the coronary thrombosis. Note the progressive clearing of the pulmonary congestion.

trast, Case 16 presented a definite but temporary increase of 2.3 cm. on the 3d day and then reversion to the original size until the 4th month when the fifth Roentgen ray showed a decrease of 1.6 cm. Case 1 presented no change in heart size until after 1 month when the fifth Roentgen ray showed a decrease of 2.4 cm. and this was maintained to a lesser degree during the rest of the observation period. In only 2 patients was there a change on the second film which was subsequently maintained, and it is notable that in 1 of these patients (Case 3) it was an increase of 2 cm. which gradually progressed to 2.9 cm. at the end of 6 months. In contrast, in the other patient (Case 5), the

change was a decrease of 1 cm. which progressed to 2 cm. in 1½ months and later regressed to 1.2 cm. Summarizing these changes in cardiac measurements it is quite evident that there was no consistent difference in heart size in this study. Eight of the patients showed no impressive change in any of their entire series of films. Of the other 8 patients showing a significant change in cardiac size, 3 presented an increase in size in one or more films, and 5 a decrease in size in one or more films. In the important first 2 weeks following the coronary accident, only 4 cases had a change in cardiac measurements and in 2 they were increased while in the other 2 they were decreased.

TABLE 1.—CHANGE IN SIZE (IN CM.) OF CORRECTED TRANSVERSE CARDIAC DIAMETER COMPARED TO FIRST ROENTGEN RAY FILM

Case No.	Number of film					
	2d	3d	4th	5th	6th	7th
1	+0.2	0	−0.9	−2.4	−1.2	−1.0
2	−0.9	−0.3	−0.7	−1.4	0	−0.1
3	+2.0	+2.1	+0.9	+2.6	+2.7	+2.9
5	−1 0	−1.1	−1.0	−2.0	−1.0	−1 2
6	+0 7	+0 4	+0.1	−0 5	−1 2	−0 4
7	−1.7	−0.9				
8	+0.9	+0.5	+0.5	+0 4		
9	−0.3	+0 2	+0.1	+0.1	+0.2	+0 2
10	0	−0 5	+0.3	+0.2	0	−0.9
11	+0.1	+0.2	0	−0.7	−0.4	−0.3
12	−0.9	+0.6				
13	+0 1	−0.1	−0.1	+0 3	+0.8	+0.3
14	0	+0.1	−0.2	−0.1	+0.2	+0.1
15	+0.8	−0.6	0	+0 2	+0.6	
16	+2 3	−0 1	+0.7	..	−1.6	

TABLE 2.—CASES SHOWING SIGNIFICANT CHANGE IN HEART SIZE IN ONE OR MORE FILMS

Case No.	Time after attack Roentgen ray taken	Change in size (cm.) of corrected transverse cardiac diameter compared to first Roentgen ray film
1	1 mo.	−2 4
	3 mos.	−1 2
	6 mos.	−1.0
2	1 mo.	−1.4
3	3 days	+2.0
	5 days	+2.1
	1.5 mos.	+2.5
	3 mos.	+2.7
	6 mos.	+2 9
	3 mos.	+1 1
5	3 days	−1 0
	5 days	−1 1
	12 days	−1 0
	1.5 mos.	−2 0
	3 mos.	−1 0
	6 mos.	−1.2
6	3 mos.	−1 2
7	3 days	−1.7
16	3 days	+2.3
	4 mos.	−1.6

An attempt was made to see if there were any features about the patients which could be correlated with the presence or absence of an increase or decrease in heart size. It is interesting that all but 1 of the 8 cases with significant change included the first 7 patients studied in the series; this might tend to suggest the fact that the technique of

taking the Roentgen rays was improved as the study was continued. However, since no change was made in the technique it is much more likely that this occurrence is merely a coincidence.   Table 3 compares the essential features of the cases which experienced a significant increase or decrease in cardiac measurements with those of the other patients.   Considering the small number of cases in each series, however, it is impossible to state that the differences indicated in these tables point to any significant feature or features which characterize patients who show an increase or decrease in cardiac size following coronary thrombosis.   Nevertheless, one point does attract attention and that is the occurrence of complications.   Five complications were met with in the entire series and 4 of these, namely, lobar pneumonia (Case 3), hemiplegia with cerebral embolus (Case 4), bronchopneu-

TABLE 3.—CHANGES IN TRANSVERSE CARDIAC DIAMETER

		Patients with significant change	Patients without significant change
Sex	Males	7	5
	Females	1	3
Age	Range	40–63 yrs.	44–68 yrs.
	Average	51.8 yrs.	60.1 yrs.
Location of infarction (from electrocardiogram)	Anterior	5	7
	Posterior	3	1
Fever	Present	8	7
	Absent	0	1
Leukocytosis	Present	7	7
	Absent	1	1
Hours after attack 1st Roentgen ray taken	Range	12–60 hrs.	20–48 hrs.
	Average	35.5 hrs.	32.5 hrs.
Heart size on 1st Roentgen ray	Normal upper limit	1	2
	Normal	3	2
	Enlarged	4	4
Change in roentgenkymogram	Present	4	2
	Absent	3	4
Lungs	Râles on phys. exam.	2	5
	Cloudiness on Roentgen ray	7	5
Blood pressure	Elevated on admission	2	5
	Elevated subsequently	0	2
Digitalis administration	. . . .	2	1
Complications	. . .	4	1
Period of observation	Range	1 wk.–7 mos.	1 wk.–6 mos.
	Average	5.1 mos.	4.5 mos.

monia followed by death after 1 week (Case 7), and pulmonary infarction with phlebitis in both lower extremities (Case 16), occurred in patients with change in heart size.   Only one complication, death from perforation of the myocardium, appeared in the other group of cases but since exitus in this patient occurred at the end of the 1st week, it is possible that succeeding films might have shown change in the cardiac measurements.   It is also interesting that 2 of the patients who received digitalis presented significant change in cardiac size, but in both cases digitalis was started on the 7th day following the coronary accident and there appeared to be no definite chronologic relationship between the beginning of digitalis administration and the occurrence of the change in measurements.   The third patient to receive digitalis did not show any difference in cardiac measurements but in this case

digitalis had been given in 0.1 gm. doses before the accident and it was continued at the same schedule following it. Aside from the complications already mentioned, it did appear that the patients with a significant increase or decrease in heart size were somewhat more ill as a group than the others. Pain and fever lasted longer in these patients, blood pressure readings following the attack fell to somewhat lower levels in the neighborhood of 90 to 110 mm. systolic and in 1 case severe attacks of angina pectoris persisted although they had been present for only 3 weeks prior to the acute episode. The only audible friction rub present in the entire series also belonged to a member of this group.

Summary. 1. The change in heart size in 16 patients following unequivocal acute coronary thrombosis was studied by teleoroentgenograms taken over periods extending from 12 hours to 7 months following the acute attack.

2. No consistent change in cardiac size or shape was noted in this study. Eight of the patients showed no change in any of their entire series of films. Each of 4 other patients presented only one film with cardiac measurements significantly different from the others of their respective series and these were taken at greatly varying intervals (3 days to 3 months) after the attack with both increasing and decreasing measurements occurring. It is noteworthy that in the important first 2 weeks following the acute accident only 4 cases of the entire series had a change in cardiac measurements and in 2 they were increased while in the other 2 they were decreased.

3. It is impossible to state from this study that there is any significant feature which characterized the 8 patients who showed a change in cardiac size following coronary thrombosis. Nevertheless, the more frequent occurrence of complications within this group attracts attention. Aside from these complications it appeared that the patients with significant change in cardiac size were somewhat more ill than the others.

4. The findings in the Roentgen ray films of pulmonary congestion in the 1st and 2d weeks following the coronary accident were especially noteworthy. Twelve patients showed roentgenologic evidence of such pulmonary involvement, whereas in only 7 of these did auscultation reveal the presence of basal râles. In 4 patients evidence of pulmonary congestion was lacking on both Roentgen ray and physical examination.

REFERENCES

1. ERNSTENE, A. C.: AM. J. MED. SCI., 178, 383, 1929.
2. FISHBERG, A. M.: Heart Failure, Philadelphia, Lea & Febiger, p. 617, 1937.
3. FOGEL, E. I.: J. Am. Med. Assn., 100, 39, 1933.
4. HORINE, E. F., and WEISS, M. M.: AM. J. MED. SCI., 189, 858, 1935.
5. PALMER, J. H.: Canad. Med. Assn. J., 36, 387, 1937.
6. SMITH, H. L., and BARTELS, E. C.: J. Am. Med. Assn., 98, 1072, 1932.
7. STEEL, DAVID: J. Am. Med. Assn., 102, 432, 1934.
8. WHITE, P. D.: Heart Disease, 2d ed., New York, The Macmillan Company, p. 357, 1938.
9. WHITE, P. D.: Heart Disease, 2d ed., New York, The Macmillan Company, p. 76, 1938.

A CASE OF MYOCARDIAL INFARCTION MASKED BY BUNDLE BRANCH BLOCK BUT REVEALED BY OCCASIONAL PREMATURE VENTRICULAR BEATS

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THE electrocardiographic signs of myocardial infarction are often obscured by intraventricular conduction disorders of high degree, especially by left bundle branch block.[2] In the following report a case is cited in which myocardial infarction associated with left bundle branch block was indicated in the electrocardiogram (E.C.G.) by ventricular premature beats, while the regular beats failed to display significant changes.

Case Report. E.S., a white male, aged 79, was admitted to the hospital on September 20, 1942. For 6 years he had suffered from pain in the chest on walking fast, especially on cold and windy days. The pain was relieved by nitroglycerine. Four days prior to admission the patient was seized by severe precordial pain and a choking sensation lasting about a half hour. Similar attacks came repeatedly and required the administration of morphine.
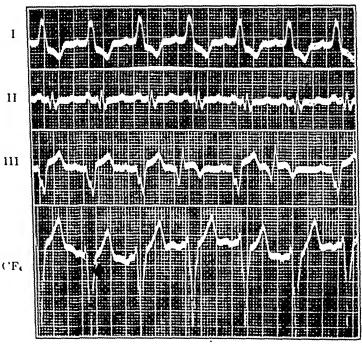
FIG. 1.—The complexes of the basic rhythm display the features of left bundle branch block. The 4th and 6th beats in Lead III are premature, followed by compensatory pauses; they have no P waves and are apparently of ventricular origin. Their shape is different from that of the regular beats, the broad Q wave preceding the R wave, an S-T segment is elevated and the T-wave inverted. These are the features usually displayed by normal beats in the presence of myocardial infarction of posterior site.

The temperature rose on the day of admission to 101° F.; the sedimentation rate (Westergren) was 39 mm. on September 24, 1942. E.C.G. examination

on September 22 and 28, 1942, revealed the signs of left bundle branch block but no significant changes suggestive of myocardial infarction. In a tracing taken October 2, 1942 (Fig. 1), 2 premature beats were observed in Lead III, apparently of ventricular origin. They had no P waves and were followed by compensatory pauses. Their shape differed from that of the regular beats, and were unusual for premature beats of ventricular origin. An R wave of moderate size was preceded by a broad Q wave of the same voltage. The duration of QRS was 0.12 sec. The S–T segment was elevated and the T wave inverted. Thus, the premature ventricular beats displayed features which are usually shown by regular beats in the presence of myocardial infarction of the posterior wall.

A diagnosis of coronary arteriosclerosis and infarction of the posterior surface of the left ventricle was made. The patient expired on October 5, 1942.

Postmortem examination revealed marked arteriosclerosis of the coronary arteries and recent thrombotic occlusion of the right circumflex branch about 4 cm. distant from its origin. There was an extensive recent infarction involving the posterior portion of the interventricular septum and the entire posterior wall of the right ventricle. In addition, numerous fibrous scars were found in the anterior and posterior walls of the left ventricle.

Excitations produced by a ventricular focus as a rule activate first the ventricle in which they originate and then spread through the interventricular septum to the other ventricle. Thus the contraction of the contralateral ventricle is delayed, as happens in bundle branch block. In fact the E.C.G. of premature ventricular beats resembles a great deal the tracing obtained in the presence of contralateral bundle branch block. However, there are exceptions. Occasionally, premature ventricular beats originate from a focus which is so located that the excitation wave may activate the two ventricles in approximately normal sequence. Then the tracing of the premature beats resembles normal complexes.[1] This may even happen when the regular beats display the features of bundle branch block.

In the presence of bundle branch block there is still another mechanism which may produce normal complexes in premature beats of ventricular origin. When, for instance, in the presence of left bundle branch block, premature beats originate in the left ventricle late in diastole at the time when the normal sinus excitation is due in the ventricles, the opposed effects of the dextrocardiogram (due to the normal excitation) and levocardiogram (due to the premature excitation) may combine to result in an approximately normal ventricular complex.[3] Such a mechanism was apparently not responsible in our case because the activation of the ventricles by the premature excitation was completed before the regular sinus excitation was due in the ventricles. The premature beats in our case were of the "intermediate type," that is, due to excitations which, because of the suitable site of the ventricular focus, activated the two ventricles in approximately normal sequence. Therefore the premature beats displayed the features of normal sino-auricular beats characteristically changed by the presence of myocardial infarction of posterior site.

Summary. A case is reported in which myocardial infarction was associated with left bundle branch block. Significant E.C.G. changes suggestive of myocardial infarction were absent in the regular beats but were displayed by premature beats of ventricular origin.

REFERENCES

1. ROTHBERGER, C. I., and WINTERBERG, H.: Zentralbl. f. Physiol., 24, 959, 1910.
2. WILSON, F. N.: Diseases of the Coronary Arteries and Cardiac Pain, edited by Robert Levy, New York, The Macmillan Company, 1936.
3. WILSON, F. N., and HERRMANN, G. R.: Heart, 8, 229, 1921.

SACCULAR ANEURYSM OF THE ABDOMINAL AORTA

REPORT OF A CASE WITH TERMINAL ANURIA AND RUPTURE INTO THE DUODENUM

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THE infrequency with which one encounters saccular aneurysm of the abdominal aorta has been repeatedly emphasized. Kampmeier's[11] report (1936) of 73 cases from New Orleans brought the published cases to 386. In 1939 Lipschutz and Chodoff[13] reported 2 cases of their own and collected 41 additional cases from the literature. Since then Bigger[2] (1940) reported 2 cases in which surgical measures were employed, with success in one instance; Kommerell and Roemheld[12] reported 2 observed during 5 years in Berlin; Huberry and Pollack[8] collected 48 cases in the Cook County Hospital records from 1926 to 1940. Allen[1] (1940) described 2 producing urologic symptoms; in 1941 Jennings[10] added 4 cases and Uhle[15] cited 4 masquerading as primary genito-urinary disease; Eliason and McNamee[4] in 1942 reported 24 cases seen at Philadelphia General Hospital in a 10 year period. In addition there have been 4 single case reports comprising 90 cases since 1939 to which we are adding one described in detail. The addition of these 91 cases to the 429 listed by Lipschutz and Chodoff brings the present tabulation (up to December 1942) to 520 cases.

In the records of the Vanderbilt University Hospital since 1925 we have found no previous cases of saccular aneurysm of the abdominal aorta in 2796 necropsies and 22,040 medical admissions.

Case Report. A white salesman, aged 59, was admitted to the medical wards on September 25, 1942, complaining of left upper quadrant pain of 6 weeks duration. He had enjoyed good health until July 1, 1942, when he suddenly experienced chills, fever, and pleuritic pain in the right chest. He entered a hospital where a diagnosis of pneumonia was made. Recovery followed chemotherapy and he was discharged after 10 days. He then felt well until 6 weeks before his admission here when he noted the abrupt onset of pain in the left hypochondrium, which was sometimes sharp and at other times cramp-like, and usually radiated toward the navel. The pain was entirely unrelated to meals or bodily movements and was not relieved by soda. Although not progressive, it had been persistent and at times was severe, requiring codeine for relief. On a few occasions he had vomited small amounts of

undigested food, but there had been no hematemesis. There had also been no change in bowel habits and no history of tarry stools. In the 3 months preceding admission he had lost 35 pounds. He had had gonorrhea 20 years previously but syphilis was denied. The remainder of the history was non-contributory.

Physical Examination. The patient showed moderate weight loss and complained frequently of abdominal pain. His temperature was 99.6° F., pulse 80, respirations 30, and blood pressure 184/106 mm. Hg. The ocular fundi revealed evidence of arteriolosclerosis with slight arteriovenous compression. The chest was emphysematous but apparently clear. The heart was not enlarged to percussion, and there were no murmurs. The aortic second sound was accentuated. Pulsations of the peripheral vessels were equal and synchronous. There was diffuse abdominal tenderness and voluntary rigidity. The liver edge was barely palpable below the right costal margin on inspiration. No other viscera or masses were felt. There was no penile scar. The remainder of the physical examination was not remarkable.

Laboratory Examination. Hematologic studies revealed: 4.76 million red blood cells per c.mm.; hemoglobin, 13.9 gm. per 100 cc.; white cell count, 14,250 per c.mm. with a normal differential. The urine appeared clear with a specific gravity of 1.018, acid reaction, a 3+ albumin, and one granular cast as well as 3 white cells and an occasional red blood cell per high-power field. The stool was negative for occult blood, and no parasites were found. The non-protein nitrogen was 34 mg. per 100 cc. The blood Kahn was positive on two occasions and negative on a third; the Wassermann reaction was repeatedly negative.

Course in the Hospital. At first it was generally thought that this patient had a carcinoma of the stomach. Roentgenographic examination of the entire gastro-intestinal tract revealed no defect. The chest film was essentially negative. The electrocardiogram indicated a normal mechanism. His course remained unchanged for a few days, although frequent administrations of codeine were necessary to allay his pain. The albuminuria continued. Phenol-sulfonphthalein excretion in 2 hours was 40%. Maximum concentration with the Fishberg test was 1.023. Urine culture was positive for *S. albus* and a non-hemolytic streptococcus, which were not considered significant.

On October 3, 1942 the abdominal pain became much more severe, and he had a chill with fever (103.8° F.). His white cell count was then 20,250. Chills and fever recurred on each of the following 2 days. He vomited frequently. No adequate explanation for these manifestations was apparent. A plain film of the abdomen on October 3 revealed no abnormality. On October 4 treatment with sulfathiazole was begun. The initial dose was 4 gm. with a maintenance dose of 1 gm. every 4 hours. The following day sulfadiazine was substituted because of increased nausea and vomiting.

On October 6 he did not void. With the thought that the anuria had resulted from chemotherapy, the drug was discontinued. The next day catheters passed to both renal pelves revealed no obstruction. Fifteen cc. of highly colored urine, obtained from the bladder, showed no sulfonamide crystals. There was no urine in the pelves, and water injected through the catheters returned clear. Parenteral fluids were forced, but they only produced peripheral edema. The non-protein nitrogen rose to 84 mg. per 100 cc. on October 7. On October 8 he was given 50 cc. of 50% dextrose intravenously, but the anuria persisted although the non-protein nitrogen had not increased significantly. On that day a lumbar puncture revealed clear spinal fluid under normal pressure with a negative Wassermann reaction.

At 1 A.M. on October 9, his 14th hospital day, he suddenly went into shock: He was semi-comatose, cold, perspiring profusely, had an ashen pallor, and his pulse was thready. Transfusion with 500 cc. of whole blood was followed by slight and temporary improvement. He then became progressively worse and died at 7.30 A.M. about 72 hours after the onset of anuria.

PATHOLOGIC FINDINGS (Dr. J. Harry Duncan): Saccular aneurysm of the abdominal aorta with thrombus formation. Compression of the left renal vein and inferior vena cava. Rupture into the third portion of the duodenum.

Gross Examination. There was about 150 cc. of blood-tinged fluid in the peritoneal cavity. The duodenum and jejunum were slightly distended, and there was a hemorrhagic discoloration with an extremely dark red line at their
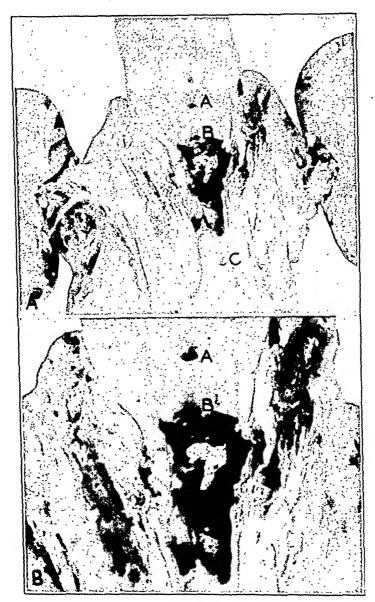
FIG. 1A.—Aorta opened posteriorly showing the aneurysm with thrombus *in situ* and orifices of (*A*) celiac axis, (*B*) superior mesenteric artery, and (*C*) inferior mesenteric artery. Orifices of renal arteries are concealed by the thrombus.

FIG. 1B.—Closer view of the aneurysm as pictured in Figure 1A.

junction with the mesentery. The ileum and large bowel did not show this change. Upon superficial examination the abdominal viscera appeared otherwise normal. The ascending portion of the aorta was slightly roughened and irregular and contained a few atheromatous plaques, but there was no associated longitudinal wrinkling or puckering.

The aorta was opened posteriorly revealing a large orifice, measuring 4 x

3 cm., in the anterior surface just below the celiac axis at the level of the superior mesenteric artery (Fig. 1). The edges of this opening were gray in color and very friable. Adjacent to this were numerous soft yellow plaques varying considerably in size and shape and containing several areas of ulceration. The entrance to the superior mesenteric artery was situated on the superior margin of this opening and was markedly distorted, presumably due to lateral dilatation of the aortic wall. The orifices of the renal arteries could not be found in the aorta. The foramen described above led into an irregular saccular dilatation measuring approximately 8 x 9 x 6 cm. In its right antero-lateral portion was a well-laminated pink-gray clot, firmly adherent to the wall and covering the orifice of the right renal artery, into which it extended for a distance of 1 to 2 cm. The orifice of the left renal artery was situated on the antero-superior margin of the sac wall and was substantially distorted and narrowed due to dilatation of the wall but contained no thrombus. There was a hemorrhagic nodular protuberance into the left side of the inferior vena cava, but the wall was intact. A perforation in the right antero-inferior margin of this sac communicated with a false pocket bounded posteriorly by the sac wall and antero-superiorly by the third portion of the duodenum where
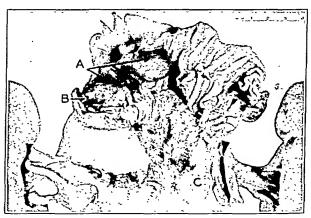
FIG. 2.—Anterior view of the aneurysmal sac and related structures. (A) Hematoma within posterior duodenal wall, (B) site of rupture, (C) anterior wall of aneurysm.

on the posterior wall there was a submucosal hematoma measuring 5 x 1.5 cm. (Fig. 2). The clot was firm, elevated, and well demarcated from the surrounding tissues and divided in its middle by a transverse groove. On the apex of the more distal elevation was a mucosal perforation 0.5 x 0.3 cm. There were no other areas of ulceration. The entire intestinal tract as far down as the sigmoid colon contained a cast of clotted blood with the marks of the intestinal folds imprinted upon it. The pancreas was rather firmly adherent about its head to the posterior wall of the aneurysmal sac but was otherwise not remarkable. Grossly the kidneys appeared normal. Both ureters were slightly dilated, but there were no mucosal lesions. The urinary bladder was not remarkable.

MICROSCOPIC EXAMINATION. (Since it was not possible to perform the necropsy until about 25 hours after death, there was a moderate amount of postmortem autolysis.)

Aorta. Sections taken at various levels, especially at the site of the aneurysm, revealed extensive atherosclerosis. The vasa vasorum exhibited marked hyaline thickening. Nowhere were there areas of necrosis in the media or perivascular accumulations of chronic inflammatory cells in the adventitia as evidence of a syphilitic aortitis.

Kidneys. The kidneys were edematous with considerable generalized tubular dilatation. There was no evidence of any significant pyelonephritis. Many of the glomeruli were filled with blood.

Prostate. Although gross examination of the prostate was not remarkable, a few small abscesses were seen microscopically.

FIG. 3

FIG. 4
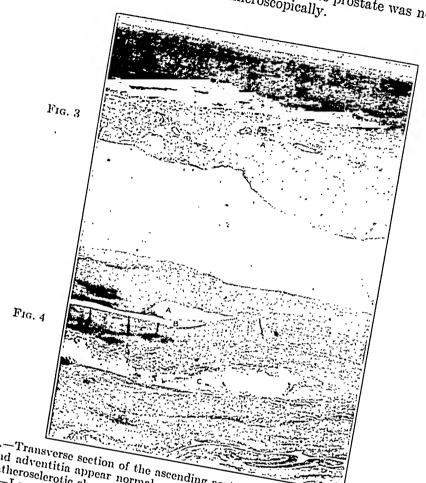
FIG. 3.—Transverse section of the ascending aorta showing slight intimal thickening. Media and adventitia appear normal. *A,* Transverse section of vasa vasorum demonstrating atherosclerotic changes. × 22.

FIG. 4.—Longitudinal section through the aneurysmal wall revealing marked intimal thickening with overlying thrombus. The clear area (*A*) represents an arteriosclerotic plaque. Note dissection between intima and media (*B*) and within the media (*C*). Adventitia is a little thickened, and there are no perivascular cellular accumulations. × 22.

Discussion. Most of the clinical symptoms and signs can be reconciled with the pathologic findings. Because of the relationship of the aneurysm to the renal arteries, it seems evident that the albuminuria was the result of interference with the renal circulation, since "it is known from animal experiments how readily even transitory interference with either the arterial or the venous supply to the kidney produces albuminuria" (Fishberg).[5] The anuria was undoubtedly also due to impairment of the arterial blood supply to the kidneys because of obstruction of the right renal artery by the intra-aneurysmal thrombus and distortion of the orifice of the left renal artery. Since the kidneys had undergone very little pathologic change, it is assumed

that there was sufficient blood flow for their nutrition but not for the maintenance of glomerular filtration pressure. The gross dilatation of the ureters and the generalized tubular dilatation might represent a partial ureteral obstruction due to compression by the aneurysm. The bacteria isolated from the voided urine specimen presumably came from the prostatic urethra, in view of the abscesses noted in the prostate and the absence of any pathologic evidence of renal infection.

There seems to be no plausible explanation for the chills, fever, and leukocytosis which occurred on his 7th, 8th, and 9th hospital days. In a case described by Held and Goldbloom[6] the repetition of chills and high fever also constituted a puzzling feature. An explanation which they offered was that the aorta perforated so slowly as to give rise to an infectious periarteritis with a localized hematoma. In our case it seems conceivable that a slow leakage of blood from the aneurysm into the gastro-intestinal tract might have led to the febrile reaction.

The abdominal pain of which the patient frequently complained may have been the result of two factors: (1) stretching the aorta, causing stimulation of autonomic pain fibers; and (2) the distortion and consequent obstruction of the orifice of the superior mesenteric artery, which could produce the syndrome of mesenteric vascular thrombosis.[13]

It is obvious that this patient did not present all the classical symptoms and signs of saccular aneurysm of the abdominal aorta. There was no palpable, pulsating abdominal mass with an associated thrill and bruit. Such suggestive roentgenologic signs as erosion of the lumbar vertebræ, a soft tissue mass, calcification in the wall of the aneurysmal sac, and displacement of viscera were not evident. Examination of the lumbar spine at necropsy revealed no erosion of the vertebral bodies.

Although syphilis is believed to be the most frequent cause of aortic aneurysm, and especially of saccular aneurysm, it is conceded that in the older age groups arteriosclerotic changes play a significant rôle in the etiology. Despite the equivocal results with the Kahn test, the absence of evidence of syphilis in the pathologic findings indicates that the aneurysm in our case was the result of arteriosclerosis.

Aneurysms of the abdominal aorta most commonly rupture retroperitoneally. Rupture into the gastro-intestinal tract is a rare occurrence. Since these aneurysms occur most frequently in the upper segment near the celiac axis, the duodenum is the usual site of perforation. Kampmeier reported 10 cases of this type including one of his own. We have since been able to collect 4 additional cases from the literature. This report brings to 15 the total number of cases of aneurysm of the abdominal aorta with rupture into the gastro-intestinal tract.

That this condition may mimic primary urologic disease, such as perinephric abscess, nephrolithiasis, and pyelonephritis, has been shown by Allen, Duchanoff,[3] Rusche and Bacon,[14] and Uhle. Hoffman[7] has recently described a case wherein compression of the left renal artery by the aneurysm was associated with a hypertension which

he attributed to renal ischemia, comparable to that produced in Goldblatt's experimental animals. James[9] has reported a case of uremia associated with a saccular aneurysm of the abdominal aorta of 4 years duration. At autopsy there was marked bilateral renal atrophy apparently due to pressure on the renal arteries and ureters by the aneurysm, although this patient had not been anuric. Our search of the literature has disclosed no previous instance in which aneurysm of the abdominal aorta has resulted in anuria.

Summary. The recent literature relating to saccular aneurysm of the abdominal aorta (520 cases) has been reviewed with especial reference to cases with rupture into the intestinal tract (15 cases) and those associated with symptoms suggesting urologic disease.

A case, apparently of arteriosclerotic origin, is presented in which there was both anuria of 3 days duration and rupture of the aneurysm into the duodenum as a terminal event.

REFERENCES

1. ALLEN, C. D.: Urol. and Cutan. Rev., 44, 462, 1940.
2. BIGGER, I. A.: Ann. Surg., 112, 879, 1940.
3. DUCHANOFF, A.: Ztschr. f. urol. Chir., 40, 34, 1934.
4. ELIASON, E. L., and McNAMEE, H. G.: Am. J. Surg., 56, 590, 1942.
5. FISHBERG, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, p. 110, 1939.
6. HELD, I. W., and GOLDBLOOM, A. A.: Surg. Clin. North America, 14, 398, 1934.
7. HOFFMAN, B. J.: J. Am. Med. Assn., 120, 1028, 1942.
8. HUBERRY, M. J., and POLLACK, S.: Am. J. Roentgenol., 43, 385, 1940.
9. JAMES, T. G. I.: Brit. J. Urol., 7, 157, 1935.
10. JENNINGS, G. J.: Lancet, 1, 719, 1941.
11. KAMPMEIER, R. H.: AM. J. MED. SCI., 192, 97, 1936.
12. KOMMERELL, B., and ROEMHELD, L.: Deutsch. Arch. f. klin. Med., 186, 136, 1940.
13. LIPSCHUTZ, B., and CHODOFF, R. J.: Arch. Surg., 39, 171, 1939.
14. RUSCHE, C., and BACON, S. K.: Brit. J. Urol., 7, 330, 1935.
15. UHLE, C. A. W.: J. Urol., 45, 13, 1941.

SURVEY OF PROTOZOAN INFECTION OF THE STAFF OF A LARGE GENERAL HOSPITAL

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THE results of surveys for the intestinal protozoan infections among hospital staffs have, as far as we know, never been published. Tsuchiya and Jean[1] (1940), in reporting the protozoan infection among freshman medical and dental students, mention that they made a survey of nurses, internes, attendants, and food handlers, but, at that time, published no results. For this reason, it was felt that a record of our survey on nurses, porters, members of the business office and others of the Graduate Hospital, University of Pennsylvania, might prove of reference value.

Material and Methods. Stool examinations were made on wet preparations, both in saline and in Lugol's iodine solutions, and on slides stained with Heidenhain's iron hematoxylin. At least 10 minutes each were spent in the examination of wet preparations and of the stained slides. Arrangements were made so that not more than 7 fresh specimens were submitted for examination in 1 day. Saline and Lugol stained smears were examined independently by both of us and the findings were combined to give the final total. For the most part, the stools had been passed less than 24 hours prior to examination. A freshly passed stool, however, is not necessarily a freshly formed stool, and trophozoites do not necessarily survive in constipated stools.

In computing our results, no infection was attributed to a particular species unless it could be verified on the stained slide. Exceptions to this were cysts of *Endamœba coli* and *Giardia*, which it was felt could be definitely determined in fresh material. Thus, although we found 136 protozoan infections, as a result of examination of both fresh and stained preparations, the species of only 114 of these could be positively identified.

Results. A total of 306 persons was examined. The following table records the incidence of infection among the group as a whole. The data are self-explanatory, and the incidence of infection is not unusual.

TABLE 1.—INCIDENCE OF INFECTION AMONG THE GROUP AS A WHOLE*

	No. of infections	Infection (%)
Total positive cases	136	44.4
Total identified cases	114	37.2
Endamœba coli	53	17 3
Endolimax nana	39	12 7
Giardia lamblia	31	10 1
Endamœba histolytica	11	3.6
Dientamœba fragilis	7	2 3
Iodamœba bütschlii	2	0.7
Chilomastix mesnili	2	0.7
Enteromonas hominis	1	0.3
Double infections	18	6.2
G. lamblia and *E. coli*	6	2 0
E. nana and *E. coli*	5	1.6
G. lamblia and *E. nana*	4	1.3
E. histolytica and *E. nana*	2	0.7
E. histolytica and *E. coli*	1	0.3
Triple infections	7	2.3
E. nana, *E. coli* and *D. fragilis*	3	1.0
E. nana, *E. coli* and *E. histolytica*	1	0.3
E. nana, *E. coli* and *C. mesnili*	1	0 3
E. nana, *E. histolytica* and *D. fragilis*	1	0 3
E. nana, *E. coli* and *G. lamblia*	1	0.3

* These numbers in each group represent only a portion of the persons employed by the hospital, since it was impossible to obtain the coöperation of the entire staff in submitting specimens. There was most difficulty with such groups as heads of departments, superintendents, internes and laboratory and social service personnel.

Each individual in the series submitted information concerning his extent of travel, past medical history, and present symptoms, if any. General good health was almost universally reported. Thus, the authors feel that symptoms may have been withheld, and that not much weight could be placed on the information presented. It was found that the extent of travel of the individuals examined had no effect on the incidence of infection.

An attempt was also made to determine the relative efficiency of wet preparations in contrast to stained slides. A comparison of the results obtained is of interest. A total of 93 infections were found on

the stained slides (M.L.), and 125 infections on fresh preparations. In the case of *E. coli*, where at times cysts may be scarce, an infection may be picked up in the fresh preparation which cannot later be found on stained slides. In our study, 23 infections of *E. coli* were found in wet preparations. On the other hand, *E. histolytica, Endolimax nana,* and *Dientamœba* (the last of which can be identified only with certainty as an "amœba trophozoite" in fresh preparations) were picked up several times on stained slides only; while 4 infections of *E. histolytica,* 5 of *Endolimax nana,* and 1 of *Dientamœba. Giardia* identification benefited from both methods; 3 were seen in wet preparations which were not found on the stained slides, while the stained method revealed 4 infections missed on the wet preparations.

Incidence of infection was recorded for the two principal race groups: negro and white. The incidence (Table 2) is somewhat higher for the whites, but not significantly so.

TABLE 2.—INCIDENCE OF INFECTION IN NEGROES AND WHITES

Race	No. of individuals examined	No. of positive cases	Infection %
Negro	93	31	33.3
White	213	83	38 3

Incidence of infection was also determined for the different occupational groups (Table 3). Most remarkable is the rather high incidence for the record room and business office.

TABLE 3.—INCIDENCE OF INFECTION IN OCCUPATIONAL GROUPS

	Nurses	Dietary dept.	Nurse's aid and maids	Porters, orderlies and elevator operators	Record room and business office
Individuals examined	81	61	55	47	40
Positive cases	30	15	20	15	23
% infection	37.0	24 6	36.3	31.9	57 5
Cases of *E. coli*	17	4	12	11	4
Cases of *E. nana*	9	7	7	2	9
Cases of *Giardia*	4	5	1	4	11
Cases of *E. histolytica*	4	1	1	2	2
Cases of *Dientamœba*	3	..	2	..	2
Cases of *Iodamœba*	..		1		
Cases of *Chilomastix*		..	1	..	1
Cases of *Enteromonas*	1				
Double infection	3	2	1	4	2
Triple infection	3	..	2	..	2

Summary. 1. Intestinal protozoan infection of 306 hospital staff members was found to be 44.4% (total identified protozoa, 37.2%; *E. coli,* 17.3%; *E. nana,* 12.7%; *Giardia,* 10%; *E. histolytica,* 3.6%; *Dientamœba,* 2.3%; *Iodamœba,* 0.7%; *Chilomastix,* 0.7%; *Enteromonas,* 0.3%).

2. Percentage infection was slightly (but not significantly) lower for negroes than for whites.

3. Incidence according to the occupations of the staff was higher, but not significantly so, in the record room and business office group.

REFERENCE

1. TSUCHIYA, H., and JEAN, J. T.: Am. J. Trop. Med., 20. 503, 1942.

PERINEPHRIC ABSCESS—A PREVIOUSLY UNREPORTED COMPLICATION OF AMEBIASIS

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A SEARCH of the American, English and Spanish medical literature fails to discover a single instance of perinephric abscess complicating amebic dysentery. Furthermore, no author has suggested the possibility that E. histolytica may be the sole cause of such a complication. The case bears so many interesting points that it will be presented in detail, but an initial review of the literature on the complications of amebic infestation with special emphasis on urinary complications is desirable.

The most frequent intestinal complications are appendicitis, massive hemorrhage, perforation of the bowel with peritonitis, amebic granuloma, cicatricial stenosis of the bowel and pseudopolyposis. Among the extra-intestinal complications, which may occur in patients with or without symptoms of amebic dysentery are amebic hepatitis, perihepatitis, hepatic abscess, lung abscess, amebic bronchitis, amebic pleurisy, cerebral abscess, splenic abscess, cutaneous amebiasis, amebecemia, amebic pericarditis, amebiasis of the vagina, uterus, ovaries, Fallopian tubes, testicles, epididymis and penis. Amebic infestation of the gall bladder and biliary system has also been reported and subdiaphragmatic collections due to E. histolytica are not a rarity. A comprehensive analysis of the surgical aspects of the complications of amebiasis has been published by Ochsner and DeBakey.[6]

The urinary complications of amebiasis are cystitis, pyelitis, nephritis, urethritis and kidney abscess. In 1913, Külz[5] reported 2 cases of multiple kidney abscesses due to E. histolytica. Hartmann-Keppel[4] (1923) recorded a case of amebic kidney abscess following the operation of a hepatic abscess, and in 1924 Vichrew[8] reported one of amebic miliary abscess in the cortex of the kidney. The most illustrative of all cases of amebic abscess of the kidney was reported by Casco[2] in 1932. It related to a 4 year old boy who had suffered from relapses and exacerbations of bloody diarrhea for months, and whose feces were positive for E. histolytica. He developed a painful and tender enlargement of the left kidney and suffered from hematuria. Later, the patient passed large amounts of anchovy sauce pus per urethra. The kidney decreased in size and trophozoites and cysts of E. histolytica were found in the pus. He was treated with emetine quite successfully. Segurola,[7] in 1932, reported a case of amebic infection of the urinary

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bladder and of the kidney pelvis, without evident intestinal infestation and without a history of amebiasis, and presenting no symptoms referable to the gastro-intestinal or urinary tracts. Goyena,[3] in 1926, reported a case of intestinal and urinary amebiasis characterized by lumbar pain, albuminuria, pyuria and hematuria.

Bernardi and Esquivel[1] (1939) made an analysis of the literature on urinary amebiasis collecting over 50 cases and adding 4 of their own. In their report, it is evident that amebiasis of the urinary tract may present numerous symptoms, but pain in the lumbar region, tenesmus on urination, pyuria and hematuria are by far the most important. They believe that urinary amebiasis is always secondary to intestinal infestation by the parasite and that it is spread either through the blood or the lymphatics. They reviewed the case reported by Ingum (1914) of a man who was suffering from chronic gonorrhea and amebic dysentery and who used the same syringe for enemas as well as for urethral irrigations. This case is illustrative of another possible mode of infection, since the patient developed amebic cystitis. In their elaborate paper, no mention was made of a perinephritic abscess due to *E. histolytica*.

Case Report. L.G., a 47 year old Italian male, was admitted to the Philadelphia General Hospital on March 6, 1942, complaining of pain in the right side of the back and on the upper abdomen. Since 1933, he had suffered from relapses and exacerbations of a bloody diarrhea accompanied, on occasions, by severe crampy abdominal pains which, in many instances, simulated appendicitis. In October, 1941, his diarrhea recurred to a moderate degree with 4 to 7 bowel movements a day which on occasions consisted of only a small amount of mucus. In late November, 1941, he developed some fever and noticed an evanescent uncomfortable feeling in the right upper quadrant with slight tenderness on pressure. At this time, a proctoscopic examination in another hospital revealed a rectal mucosa which bled easily, but presented no ulcerations and a barium enema demonstrated irritability of the colon. In December, 1941, he was taken with severe constipation which persisted until time of admission, and his pain in the right upper quadrant increased in severity. No weight loss, but marked weakness was recorded. His social history revealed that at the time of onset of his illness in 1933, he was employed digging a well in southern New Jersey. No history pertaining to traveling was obtained.

On physical examination, at the time of admission, his temperature was 101° F., pulse 90, respirations 23, blood pressure 120 systolic, 70 diastolic. He appeared quite ill and showed marked pallor of the skin and mucous membranes. The costal margin flared more on the right than on the left, and the diaphragmatic excursions were diminished on the right side. Percussion note was flat at the right base up to the angle of the scapula with suppression of breath sounds in that area. Râles were heard on the left base posteriorly. There was a visible fulness in the right upper quadrant. The liver apparently extended 17 to 18 cm. below the 5th rib. It and the right costovertebral angle were exceedingly tender. Peristalsis was exaggerated and puffing and whistling in type. The rest of the physical examination was essentially negative.

Course. The temperature varied between 100° and 102° F. The blood picture on March 6, 1942 revealed a moderate secondary anemia and white cell count of 9600, of which 80% were neutrophiles, 15% lymphocytes, 2% monocytes and 3% eosinophiles. Five days after admission his blood picture was unchanged except for a left shift with a Schilling index of 1.9. The prothrombin time was 45% of normal. The stool examination was negative for *E. histolytica*. Roentgenographic studies revealed a slight elevation of the

right diaphragm with haziness at the base of the right lung. The liver was reported not enlarged.

Eight days after admission, laparotomy (Dr. E. L. Eliason) showed that the liver was diffusely enlarged, but no pus or intrahepatic or subdiaphragmatic masses were encountered. The gall bladder wall was thick and edematous, but no stones were palpable. The pancreas was normal. On the retroperitoneal surface, just below the liver, the tissues were dense, thickened and edematous and fluctuation was elicited. By blunt dissection carried around retroperi-
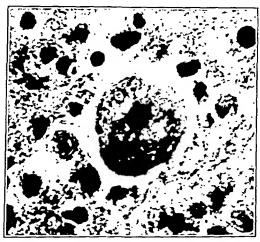
Fig. 1.—*Entamœba histolytica* trophozoite. Stained paraffin section of pus from *perinephritic abscess showing two ingested erythrocytes.* (× 1500.)
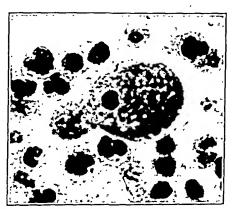
Fig. 2.—*Entamœba histolytica* trophozoite. Paraffin section of pus from perinephritic abscess. Note pseudopod. (× 1500.)

toneally to the perinephric space, a large collection of pus was opened and drained. The cavity occupied the entire perinephric space. The pus was thick and yellow, and was drained through a lateral stab-wound. Examination of the fresh pus failed to reveal any amebæ.

Postoperative Course. Considerable amounts of mucoid, blood-tinged, foul-smelling pus drained for a long time from the lateral portion of the incision. Cultures were positive for *Staph. aureus* and *Esch. coli*. Repeated examination of the pus failed to show *E. histolytica* cysts or trophozoites. Lipiodol visualiza-

tion of the abscess cavity localized it in the region of the 12th rib extending somewhat anteriorly and downwards to the level of the 2d lumbar vertebra. Intravenous urograms showed no abnormalities.   Ten days after operation,
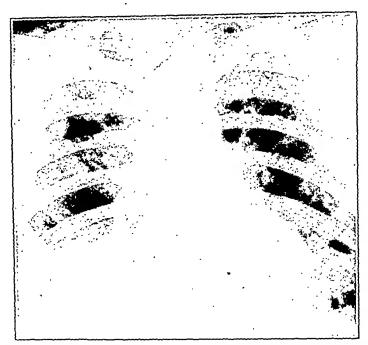
FIG. 3.—Preoperative chest film showing slight pleural reaction above and slight elevation of right diaphragm.
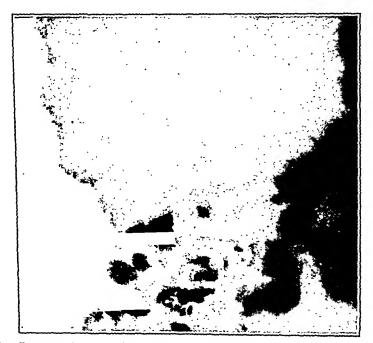
FIG. 4. --Preoperative flat plate of abdomen showing some hepatic enlargement.

blocked paraffin sections of the pus revealed *E. histolytica* in the vegetative forms and this finding was confirmed 3 days later. (This method is totally reliable, and the diagnosis of the condition cannot be questioned, in spite of the fact that the parasite was not found on fresh mounts.) (See Figs. 1 and 2.)

The temperature dropped to normal on the 3d postoperative day, flared up on the 23d and leveled off at 100° F. on the 36th day. Forty-six days after the operation, a course of emetine hydrochloride was started consisting of a hypodermic injection of 1 gr. of the drug daily for 12 days; this was repeated after a 2 weeks' rest. The abscess cavity was irrigated with emetine hydrochloride on several occasions. A course of vioform followed, and no amebæ were seen in the pus. No amebæ were found in the stools during or after completion of chemotherapy.

The patient improved remarkably fast after treatment, drainage ceased and he was discharged 131 days after admission and 123 days after operation.

Fig. 5.—Antero-posterior view of abdomen following lipiodol instillation into abscess cavity. The abscess is visualized laterally.

Comment. In the analysis of this case, it is evident that the patient suffered from a dysenteric form of amebiasis since 1933, as suggested by the relapses and exacerbations of bloody diarrhea; and that apparently there was involvement of the cecum and appendiceal regions by *E. histolytica*, since the patient had frequent attacks of pain in the right lower quadrant simulating appendicitis. Fever and dull pain in the right upper quadrant in November, 1941, obviates the supposition that he may have had a hepatitis secondary to the amebic colitis, or perhaps this was the initial symptom of the perinephritic collection of pus. The latter supposition is substantiated by the fact that the symptom picture in the right upper quadrant progressively increased

in severity. It can be assumed that the patient may have been suffering from the perinephric collection of pus since November, 1941. The first impression was that this patient was suffering from a subdiaphragmatic or hepatic abscess. There was, nevertheless, exquisite tenderness in the right costovertebral angle, which may have suggested kidney involvement. The blood picture of this patient did not suggest a purulent process, as there was a leukocytosis of only 9600. Examination of the liver and subdiaphragmatic space failed to reveal abscess formation. The thickness and swelling of the gall bladder wall is difficult to explain on the basis of an amebic infection. The dense wall and fibrosis of the perinephric abscess suggested a chronic course, but the character of the pus, on operation, was not typical of amebic infection. The failure to find the ameba in fresh mounts of the pus is not explained. The prolonged draining from the surgical incision may have been due to amebiasis of the tissues surrounding the wound, this being suggested by the rapid improvement after treatment with emetine hydrochloride.

As to the origin of the *E. histolytica*, we do not doubt that it was from the colon, but how it got to the perinephric space is difficult to state. Nevertheless, there are four possibilities for such a phenomenon. The patient may have had a hepatic abscess which ruptured into the perinephric space, but this is not evidenced by the findings on surgical exploration and it is a known fact that the majority of the hepatic abscesses due to *E. histolytica* rupture through the diaphragm into the pleural cavity. There is the possibility that this was a hematogenous metastasis, but we doubt it, since the parasite had to be filtered through the liver and lungs, and an abscess of the liver would have developed. The parasite may have been carried by the blood stream from an amebic infection of the lungs or bronchi, but this is hardly possible as there was no evidence of lung or bronchial involvement in the process, and this was a very strange localization for a blood-borne infection of this nature.

The last and strongest possibility is that the parasite may have passed through the lymphatics and localized in the perinephric space. The opinion is divided as to the lymphatic metastasis of amebic lesions, but Bernardi and Esquivel[1] are certain of its possibilities.

Summary. 1. A perinephric abscess—due to *E. histolytica*, apparently the first case—is reported. The diagnosis was proven by the demonstration of the parasite in the pus draining from the abscess after surgical intervention.

2. There is no doubt that there was involvement of the appendix and sigmoid, since the patient suffered from pain in the right lower quadrant suggesting appendicitis.

3. The complication was ushered in by a progressively severe pain in the right upper quadrant and pain in the right costovertebral angle.

4. The patient was explored and no evidence of a hepatic or a subdiaphragmatic abscess was found.

5. It is possible that the parasite traveled through the lymphatics and localized in the perinephric space.

REFERENCES

1. BERNARDI, R., and ESQUIVEL, R. B.:   Semana méd., **1**, 248, 1939.
2. CASCO, E. D.:   Rev. méd. latino. Am., **17**, 1165, 1932.
3. GOYENA, J. R.:   Semana méd., **1**, 1075, 1926.
4. HARTMANN-KEPPEL: Bull. et mém. Soc. de chir., Paris, **49**, 216, 1923.
5. KÜLZ, L.:   Arch. Schiffs u. Tropen-Hyg., **17**, 273, 1913.
6. OCHSNER, A., and DEBAKEY, M.:   New Internat. Clin., **1**, 6S, 1942.
7. SEGUROLA, M.:   Vida Nueva, **20**, 24, 1927.
8. VICHREW, P.:   Med. Ges. Tiflis, January 24, 1924.

PROGRESS

OF

MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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GAS GANGRENE

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In 1607 Fabricus Hildanus[36a] described a case of gas gangrene. Few clinical descriptions of the disease since that time have been clearer:

"On the 21st July, 1607, Estienne Topin wished, as work in the harvest reached its height, to lead himself an empty cart. He was at the time fifty years old, of robust build and in the best of health. As he was running he fell and the wheel of the cart tore up the whole of the inner part of the leg. The periosteum was ripped from the tibia for a palm's length; neither bone was, however, broken or cracked so that he was able to walk to his home about half an hour's walk away. . . . I was called the very same day: I anointed the whole of the thigh with oleum rosar and having washed the wound with red wine and tepid water . . . I enveloped the whole of the leg in a bandage soaked in vinegar . . . he had a restless night . . .

"On the 23rd . . . on removing the bandage it was seen that the part of the calf which had been separated from the underlying flesh required excision since it was turning livid and about to become gangrenous. I accordingly cut off this part . . . and having washed the stump with vinegar and salt I dressed it . . . and applied (a) poultice . . .

"On the morning of the 24th I undid the bandages and it was perfectly clear that the putrefaction had been arrested and that the gangrene was not spreading. . . . In the afternoon he was seized with an intense pain in the outer part of the leg . . . yet there was no outward sign and no obvious inflammation.

"On the 25th . . . I undid the dressings and found the external parts of the calf were black and mortified over a palm's width. . . . About midday . . . removing again the bandages I found the whole of the outer part of the leg and the foot itself mortified and covered with large black vesicles containing water similar to that in which meat had been washed: in certain places great pain persisted . . . Furthermore as I began to shave off some of the hair above the knee on the outer aspect at a certain place I could make out a sound as if there were some sort of empty space underneath. Inferring, therefore, that the disease was present underneath in that place I began to explain . . . that amputation was clearly going to prove fruitless . . . Two hours later . . . I saw that the place

about which we had heard the sound had become completely mortified. About ten that evening a vesicle the size of an egg arose in his groin beside the scrotum, black and filled with water like meat washings. On opening this the underlying flesh was black and gangrenous: within the next two hours the scrotum became swollen the size of a head and gangrenous. At about the third hour after midnight he became covered with sweat, at first hot then cold, and he died peacefully, in the middle of a sentence, four days, eleven hours after his illness commenced, and twenty-four hours after the onset of the gangrene."

Gas gangrene has generally, although not always, been a companion of wars. In the British armies in France in September 1914, between 10 and 12% of the wounded developed gas gangrene. Four years later the incidence had fallen to less than 1% of the wounded, as stated by the British Medical Research Committee Report on Anaërobic Infection.[56] In the French and German armies the incidence appears to have been slightly higher.[12,83] It was always found that the incidence was highest in periods of active operations when there was greatest delay in collection of the wounded. In civilian life the incidence is probably lower, though there are few data. Cramp (1912)[15] states that among 5802 accident cases in New York, 1909 to 1912, there were 9 cases of gas gangrene (0.16%).

1. The Etiology of Gas Gangrene. The relationship of the *Clostridia* to gas gangrene was long in confusion. Pasteur and Jobert (1877)[68] described *Vibrion septique* (*C. septicum*), and 4 years later Koch (1881)[40] described what he believed to be the same organism which was known in Germany as Koch's *Bazillus des malignen Oedeme*. Chauveau and Arloing's (1884)[13] study of gas gangrene appeared to indicate that it was a specific disease caused by this organism. But Welch and Nuttall (1892)[102] isolated *B. aerogenes capsulatus* (*C. welchii*) from gas gangrene cases and produced the disease in experimental animals. Within the next few years Welch's organism was rediscovered in both Germany and France. Fränkel in Germany called it *B. phlegmonis emphysematosæ*, and Viellon in France called it *B. perfringens*.

TABLE 1.—INCIDENCE OF VARIETIES OF GAS GANGRENE BACILLI

France—War 1914-18

	Weinberg and Séguin 91 cases, %	McIntosh 93 cases, %	Henry 50 cases, %	Germany peacetime 21 cases, %	Argentina 11 cases, %
C. welchii	71	55	80	100	46
C. novyi	34	4	10	33	10
C. septicum	13	16	16	5	27
C. sordellii	?	?	?	?	18
C. fallax	16	.	6	.	18
C. histolyticum	.	.	.	5	18
C. sporogenes	27	37	..	?	64

With the studies on the group carried on during the last war, order began to emerge. It became apparent that gas gangrene may be caused by one or a group of species of *Clostridia*. The distribution of species in gas gangrene infections is suggested in Table 1. The difference in the findings of different observers probably results from great diversity in occurrence of the species and in part it is due to different methods of isolation and identification used by the several observers. Moreover, these infections usually yield more than one species of *Clostridia*. In 37 of Weinberg and Séguin's (1918)[95] 91 cases of gas gangrene only 1 species of *Clostridia* was isolated; 29 *C. welchii*, 5 *C. novyi*, 1 *C. septicum*, 1 *C. fallax*, 1 *C. aerofœtidum*. In 54, approximately half the 91 cases, 2 or more species of *Clostridia*

were present and frequently also streptococcus, staphylococcus or other aërobic species.

2. Cultivation of Clostridia.   The pathogenic *Clostridia* grow luxuriantly on a wide variety of culture media.   Most species are able to utilize complex proteins or obtain their nitrogen from peptones, amino acids or simpler nitrogen compounds.   Many species will utilize glycerol, starch or a variety of sugars.   The older types of media were rich in proteins: chopped meat, liver or egg.   The modern trend is toward media consisting of simple peptones—sugar solutions or synthetic mixtures.

The conspicuous feature of this group is the intolerance to oxygen. This necessitates cultivation either in an atmosphere with a low partial pressure of oxygen or in a medium poised at a negative oxidation-reduction potential.   The degree of oxygen intolerance varies widely from species to species.

(*a*) *Surface Growth.*   The most conspicuous landmark in the technique of the study of this group was the introduction of the McIntosh-Fildes anaërobic jar.[20a,21,53,59]   Older procedures used for surface plating while generally successful gave variable results due largely to irregularities in oxygen pressure.   If plates are inoculated from a wound exudate, for example, and incubated in an atmosphere of only moderately low oxygen tension, the more oxygen-tolerant species like *C. welchii* may grow while the oxygen intolerant species like *C. tetani* may fail to grow, thus leading to erroneous conclusions and frequently interfering with the isolation of pure cultures.

Many modifications have been made in the original Fildes' jar; Brewer's (1941)[8,9] jar is mechanically excellent, but the original principle remains unchanged.   Two considerations are essential—the jar must be capable of holding a vacuum and means must be provided for keeping the platinized or palladinized asbestos catalyzing element dry and preferably heated when in action.

(*b*) *Growth in Fluid or Semisolid Media.*   Cultivation of *Clostridia* in fluid media is much simpler than on the surface of solid media.   The older unsatisfactory method of driving out dissolved oxygen by boiling and covering the surface of the medium with a layer of oil has largely given place to media poised at or near the optimum oxidation-reduction potential in which cultures are incubated exposed to air.   This objective is achieved in chopped meat media,[42] or clear media may be adapted by the addition of suitable reducing agents and a trace of agar.   The procedure of adding reducing substances has long been followed to a limited degree and many agents have been suggested.[1]   The use of agar to retard oxygen diffusion has also frequently been suggested.[90b]   Brewer (1940)[9] combined the use of highly efficient reducing agents, sodium thioglycolate or sodium formaldehyde sulfoxylate with a small concentration of agar.   McClung (1940)[49b] and Reed and Orr (1941)[75c] have shown that all the known pathogenic species of *Clostridia* grow luxuriantly from small inocula in such media.

The optimum or limiting O/R potential for the various species has never been established, though Quastel and Stephenson (1926)[73] and Fildes (1927, 1929)[20b,c] have approached the points probably as closely as the complexity of the system will permit, and Reed and Orr (1943)[75g] have shown that all the known pathogenic species of *Clostridia* will grow from a minute inoculum in a simple peptone medium poised at an O/R potential level of Eh −100 to −200 volts.

Media prepared along these lines have given good results in biochemical reactions for the identification of *Clostridia*. (See Appendix.)

3. Proposed Procedure for Isolation of Clostridia From Wound Exudates. The following procedure has been in use in this laboratory for some years.[75c] It is in no way unique. It merely outlines a method which has generally given satisfactory results in a short period.

Swabs or fragments of tissue from an infected wound suspected of containing gas gangrene or tetanus organisms are smeared and stained by Gram's method* and are cultured as follows:

(*a*) Tubes of chopped meat medium are heavily inoculated. These are subsequently used only if the primary plating fails.

(*b*) Swabs or fragments of tissue are introduced into 8 ml. tubes of peptone-thioglycollate broth, well mixed, and 1 to 10, 1 to 100 and 1 to 1000 dilutions are made in similar broth. Generally less growth is obtained when saline solution is used for this purpose.

(*c*) From each dilution surface plates are then made on blood agar, clear peptone-thioglycolate agar and pour plates in semisolid thioglycolate agar. All are incubated in a Fildes type anaërobic jar. It frequently aids colony selection if a few plates are also incubated aërobically. The greatest difficulty in plating arises when spreading types are present. The worst offenders are of course *C. tetani* and species of *Proteus*, but *C. sporogenes*, *C. bifermentans* and even *C. septicum* at times are troublesome. This tendency is considerably reduced if the surface of the medium is kept relatively dry. Since moisture accumulates in the anaërobic jars, drying the plates before inoculation is of little aid. Better results are obtained by placing calcium chloride or "Dessigel S" in the anaërobic jars. We use a Petri dish cover about half filled with granular calcium chloride in the bottom of the jar and, in a deep jar with 12 to 14 plates, a second, similar dish of calcium chloride on the top of the pile of plates. The use of sodium azide as proposed by Lichstein and Snyder (1941)[43] to inhibit the growth of *Proteus* may be an advantage.

Subsurface growth in soft agar, as was shown by Greenberg (1941),[25] tends to be more discrete than surface growth on firm agar. If the inoculation is too heavy the growth may be diffuse, or, in the case of *C. tetani*, delicate irregular threads of growth may appear through the agar which are detectable only in a very clear medium with a good magnification. When the inoculum is light, even *C. tetani* and *Proteus* generally form discrete colonies.

Surface and subsurface colonies reach their maximum growth in 24 to 72 hours. If the media and the jars are satisfactory, colonies are distinguishable and may be fished at 18 to 24 hours.

COLONY FORM. Colonies of the members of the genus *Clostridium* have been described and figured by many authors, particularly Weinberg, Nativelle and Prévot (1937).[101] They may be considered as belonging to five fairly clearly defined groups, as follows:

COLONY FORM A: Large raised colonies, smooth to slightly folded, with entire or undulate margins, ordinarily reaching 2 to 4 mm. in diameter. The subsurface colonies are lenticular and entire or slightly irregular. Frequently smooth bulges appear on otherwise perfect lens-shaped colonies.

C. welchii is the most characteristic species of this group. Ordinarily the surface colonies are perfectly smooth and entire, though frequently the

* In using Gram's stain on members of this genus it is important, as shown by Spray (1936),[135] to decolorize with alcohol and not with acetone or alcohol and acetone. The latter procedures give irregular results.

margins are slightly undulate. The subsurface colonies are perfectly lens shaped to slightly irregular, *C. butyricum*, *C. multifermentans*, *C. aerofœtidum* and *C. paraputrificum* develop in similar colonies, but ordinarily the surface is slightly folded and the margins undulate.

COLONY FORM B: This type is represented by smaller, raised colonies, smooth to slightly folded or irregular, with entire to undulate or serrate margins, ordinarily reaching 1 to 2 mm. in diameter. The subsurface colonies are lenticular and are smooth to irregular, with short, thick rhizoids. This is the characteristic form of *C. tertium*, *C. carnis*, *C. sphenoides* and *C. difficile*.

COLONY FORM C.: This form is represented by one species in the group, *C. histolyticum*. The colonies are minute, raised, smooth and entire to slightly irregular with short rhizoids, ordinarily 0.1 to 0.2 mm. in diameter. The subsurface colonies are spherical to lenticular and entire to irregular, with short rhizoids.

COLONY FORM D: With this type there are moderate to large colonies, raised, irregular, with widespreading coarse rhizoids, 1 to 5 mm. in diameter. Subsurface colonies are occasionally spherical or lenticular, with widespreading rhizoids to irregular rhizoid masses. Colonies of the several species which grow in this form vary in respect to average size and extent of rhizoid spread: *C. cochlearium* and *C. tetanomorphum* colonies are small, 1 to 2 mm., with spreading fine rhizoids; *C. fallax* colonies are larger, 2 to 3 mm., with rather coarser rhizoids; *C. septicum* and *C. novyi* colonies are 2 to 4 mm., with rather coarse rhizoids.

C. sordellii and *C. bifermentans* tend to grow in still larger colonies with irregular margins and folded surfaces, generally without widespreading rhizoids, but some strains produce fimbriate colonies resembling those of *C. septicum*. Subsurface colonies are generally rectangular, frequently occurring in aggregates.

COLONY FORM E: This type is represented by *C. tetani*. Surface growth varies from irregular granular colonies with delicate spreading rhizoids to irregular spreading rhizoids without any definite formed colony structure. Subsurface colonies are irregular spherical masses with widespreading, very delicate rhizoids to single irregular rhizoid-like structures.

The usual colony form of the gas gangrene group is indicated in Table 2.

Surface growth on blood agar plates or subsurface growth in the 0.75% agar plates containing blood develop colony forms in general similar to those in clear peptone-thioglycolate media. For the most part, growth on or in blood agar is slightly more luxuriant, but the particular advantage is the hemolytic reaction. As is indicated in Table 2, all the toxin-producing species produce a zone of clear hemolysis about the colonies, somewhat more definite about subsurface colonies. The non-toxin-forming species do not produce hemolysis, with the exception of *C. sporogenes*, which ordinarily produces a narrow zone of partial hemolysis.

The most distinctive reaction occurs in the case of *C. welchii*. This organism ordinarily produces a double zone of hemolysis—an inner zone of complete clearing of the medium 5 to 10 mm. wide and an outer zone of partial hemolysis about 2 to 3 times as wide as the inner clear area. This double zone is apparent in a medium containing whole or defibrinated blood but not when preserved blood[74] or citrated blood is used.

It must be kept in mind that colony structure, especially when one is working from old laboratory strains, may be most deceptive. It was shown by Orr, Josephson, Baker and Reed (1933)[64] and by McGaughey (1933)[52] that *C. welchii* readily varies from S to R and that the R colony has more

the form of a *C. sporogenes* or *C. bifermentans* colony than the normal S form of *C. welchii.* Hoogerheide (1937)[34] found the same type of variation to occur with *C. histolyticum,* while Sordelli and Ferrari (1930)[89] and Spray (1933)[90a] briefly describe similar changes in several species in this group.

TABLE 2.—SURFACE COLONIES IN 24 HOUR CULTURES ON PEPTONE-THIOGLYCOLATE OR BLOOD AGAR AND SUBSURFACE COLONIES IN SEMISOLID AGAR; MORPHOLOGY OF ORGANISMS FROM THE SAME 24 HOUR CULTURES OR FROM PEPTONE-THIOGLYCOLATE BROTH

Species	Colony form (see text)	Hemolysis	Rods	Spores
Cl. welchii	A	+ double zone	Short, thick, capsulated	Very rare; oval, subterminal
Cl. butyricum	A	....	Short, to long, thick	Oval, excentric to subterminal, swelling
Cl. multifermentans	A	....	Short to long, thick	Oval, central to excentric, swelling
Cl. aerofœtidum	A	....	Short	Very rare; oval, subterminal
Cl. tertium	B	....	Short to long, slender	Rare; oval, terminal, swelling
Cl. fallax	D	....	Short to long, thick	Very rare; oval, subterminal, swelling
Cl. paraputrificum	B	....	Short to long, thick	Rare, spherical, terminal, swelling
Cl. carnis	B	+ single zone	Short, thick	Oval to elongated, terminal
Cl. chauvœi	D	+ single zone	Short to long	Oval, excentric to subterminal, swelling
Cl. septicum	D	+ single zone	Short to long	Oval, excentric to subterminal, swelling
Cl. sphenoides	B	....	Short, oval to fusiform	Rare; spherical, terminal, swelling
Cl. novyi	D	+ single zone	Short to long	Large oval, subterminal, swelling
Cl. bifermentans	D	....	Short, thick	Oval, excentric to subterminal
Cl. sordellii	D	+ single zone	Short, thick	Oval, excentric to subterminal
Cl. sporogenes	D	± single zone	Short to long filaments	Oval, excentric to subterminal, swelling
Cl. histolyticum	C	+ single zone	Short to long	Oval, subterminal, swelling
Cl. tetanomorphum	D	± single zone	Short to long, slender	Spherical, terminal, swelling
Cl. difficile	B	+ single zone	Short to long, thick	Oval, elongated, subterminal, swelling
Cl. capitovalis	B to C	...	Short, slender	Oval, terminal, swelling
Cl. cochlearium	D	..	Long, very slender	Oval, terminal, swelling
Cl. tetani	E	+ single zone	Short to long, slender	Spherical, terminal, swelling

In our experience only S forms have been isolated from infected wounds—the aforementioned studies have shown that S to R variation is accompanied by a decrease in virulence. It is perfectly possible, however, that variant types may be found in infections.

(*d*) *Isolation.* In identifying organisms from the primary plates, single colonies are fished from the primary surface plates in the ordinary manner. A single large colony, such as that characteristic of *C. welchii,* provides ample material for the inoculation of the necessary diagnostic media. In the case of minute colonies like those of *C. histolyticum* it is an advantage to fish a single colony to a small deep tube of peptone-thioglycolate medium and incubate for a few hours.

In fishing minute subsurface colonies from a semisolid medium it is frequently an advantage to use a glass tube drawn out to a fine tip. After one has determined that the selected colony is free from spreading growth, which generally can be done with a 25 diameter binocular microscope and a subdued illumination from below the plate, the colony is stabbed with the capillary tube. The tube is then broken in the bottom of a peptone-thioglycolate broth tube.

The 10 tubes of diagnostic media, described in the following sections and listed at the top of Table 3, are then inoculated together with a plate of milk agar and preferably with additional plates to establish the purity of the cultures. Inoculation of a medium in a deep tube is most effectively done with a Pasteur pipette which delivers a few drops of inoculum at the bottom of the tube.

In many instances it will be possible to obtain pure cultures of *Clostridia* from the first plating of wound exudates, *i. e.*, in 24 hours. Frequently replating will be necessary.

4. Rapid Identification of Clostridia. As generally carried out the identification of species of *Clostridia* is a protracted process. We are of the opinion that, once a pure culture has been obtained, the newer types of cultivation permit as rapid identification as in most other groups of bacteria (Reed and Orr, 1941[75c]).

The 5th edition of "Bergey's Manual" recognizes some 51 species belonging to the genus *Clostridium*. These may be roughly divided into four subgroups:

(1) Gas gangrene groups and related species, 20 species.
(2) Tetanus group, 1 specie.
(3) Botulinus group, 2 species.
(4) Non-pathogenic group, 28 species.

This article deals entirely with the first group.

A. *Biochemical Reactions.* Table 3 summarizes a series of biochemical reactions of most value in establishing identity of members of the gas gangrene group.

TABLE 3.—BIOCHEMICAL REACTIONS OF GAS GANGRENE CLOSTRIDIA

Species	Milk	Dextrose	Maltose	Lactose	Salicin	Sucrose	Hydrogen sulfide	Gelatin liquefaction	Nitrate reduction	Indol	Milk agar digestion	Exotoxin
Cl. welchii (perfringens)	Stormy	+	+	+	−	+	+	+	+	−	−	+
Cl. butyricum (group)	Stormy	+	+	+	+	+	−	+	+	−	−	
Cl. multifermentans	Stormy	+	+	+	+	−	+	+	+	−	−	
Cl. aerofoetidum	Stormy	+	+	+	+	−	+	+	+	−	−	
Cl. tertium	Acid	+	+	+	+	+	+	−	+	−	−	−
Cl. fallax	Acid	+	+	+	+	+	+	−	+	−	−	+
Cl. paraputrificum	Acid	+	+	+	+	+	±	−	−	−	−	
Cl. carnis	Acid	+	+	+	+	+	+	−	−	−	−	+
Cl. chauvoei	Acid	+	+	+	−	+	+	+	+	−	−	+
Cl. septicum	Acid	+	+	+	+	−	+	+	+	−	−	+
Cl. sphenoides	Acid	+	+	+	+	−	+	−	+	+	−	−
Cl. novyi (oedematiens)	Digested	+	+	−	−	∼	+	+	−	−	±	+
Cl. bifermentans	Digested	+	+	−	−	−	+	+	−	+	+	+
Cl. sordellii	Digested	+	+	−	−	−	+	+	−	+	+	+
Cl. sporogenes	Digested	+	+	−	−	−	+	+	−	+	+	+
Cl. histolyticum	Digested	∼	−	−	−	−	+	+	−	−	+	+
Cl. tetanomorphum	No change	+	+	−	−	−	±	−	−	−	±	−
Cl. difficile	No change	+	−	−	+	−	−	−	−	−	−	+
Cl. capitoralis	No change	+	−	−	−	−	±	±	−	+	−	+
Cl. cochlearium	No change	∼	−	−	−	−	±	±	−	+	−	+
Cl. tetani	No change	∼	−	−	−	−	+	±	−	−	−	+

1. MILK. The gas gangrene group may most readily be divided into two main divisions on the basis of reaction in milk, *i. e.*, those which produce "stormy fermentation" and those which do not. Milk containing reduced iron (see Appendix) permits this distinction to be made in 18 to

24 hours. As is indicated in Table 3, stormy fermentation is produced by *C. welchii*, *C. multifermentans*, *C. aerofœtidum* and *C. butyricum*.

Further separation on the basis of milk reactions is not so clear cut, but, as is indicated in Table 3, some 9 species form acid, which generally does not reach sufficient concentration in 24 hours to cause coagulation. Bromcresol purple shows an acid reaction. Three other species, *C. bifermentans*, *C. sordelli*, *C. sporogenes* and generally *C. novyi* and *C. histolyticum* give evidence of digestion in 24 hours, though in most instances the reaction is not complete before 48 hours or longer. The remaining four species, though they grow in milk, produce no reaction.

2. Sugar Fermentation. The most significant diagnostic differences in sugar fermentations are seen in the reactions to dextrose, maltose, lactose, salicin and sucrose. In the peptone-thioglycolate medium just described, if fermentation occurs, sufficient acid will have formed to give added bromthymol blue a frank yellow color in less than 24 hours, while sugar-free control cultures remain blue to the indicator. Since the indicator tends to be reduced by these organisms, it is necessary to add it at the end of the growth period and to read the reactions fairly promptly.

It is apparent from Table 3 that the stormy milk fermenters, with two exceptions, ferment all 5 sugars. Of those species which form acid in milk, the first 3 listed in the table, *C. tertium*, *C. fallax* and *C. paraputrificum*, ferment all 5 sugars. *C. carnis*, *C. chauvœi*, *C. septicum* and *C. sphenoides* ferment 4 of the 5, though they do not attack the same 4 sugars. Four species which digest milk ferment only dextrose and maltose, while *C. histolyticum* ferments no sugars. Of those which produce no change in milk, *C. tetanomorphum* and *C. difficile* ferment 2 sugars, while *C. cochlearium* and *C. tetani* ferment no sugars.

3. Hydrogen Sulfide. All species in this group produce some hydrogen sulfide when sulfur compounds are supplied in suitable form (Pacheco and Costa, 1940). The proteose peptone medium with bismuth or lead (see Appendix) as an indicator is definitely darkened or blackened in 24 hours by 17 of the 21 species in the group. *C. tetanomorphum* and *C. tetani* darken but do not generally blacken the medium in 24 hours, while *C. multifermentans*, *C. carnis*, *C. capitoralis* and *C. cochlearium* fail to cause any darkening of these media in 24 hours. The differentiation which Spray (1936)[90b] made between *C. tertium* and *C. fallax* on the amount of hydrogen sulfide produced is not apparent on these media.

4. Liquefaction of Gelatin. About half the species in this group produce rapid liquefaction of gelatin (see Appendix). The procedure has been to incubate the cultures at 37° C. and to test for liquefaction after the culture has stood for an hour in an ice-water bath.

5. Reduction of Nitrate. In the medium described (see Appendix) about one-third of the species in the group produce nitrites. The remaining species apparently fail to reduce the nitrate, as is shown by the fact that no nitrites are detectable at 24 hours. No distinction is made here between those species which fail to attack nitrate and those which break down nitrite as it is formed.[78]

6. Indol. In the tryptophane-containing medium described (see Appendix) about one-third of the species in the group produce indol, the remainder apparently failing to do so. No distinction is made here between those species which fail to break down the tryptophane and those which split the indol as it is formed.[75]

B. *Morphology.* The morphologic character of the organisms in this group as observed in 24 hour cultures on blood agar, peptone-thioglycolate

agar or peptone-thioglycolate broth is not distinctive. Sporulation, when present, is characteristic; but it is frequently absent even in cultures which sporulate freely 48 to 72 hours later. Smears from the young cultures, however, when well stained by Gram's stain without acetone, aid in checking the purity of cultures and frequently supplement the biochemical differentiation of species (Table 2).

A few cultures generally give atypical reactions: A few strains of *C. welchii* fail to give a positive nitrite reaction. As shown by Reed (1942)[78] this is due to the reduction of nitrites to ammonia.

In a few instances it has been impossible to distinguish between *C. septicum* and *C. chauvoei.*

A few *C. novyi* fail to ferment maltose in 24 hours.

A few *C. tetani* fail to produce hydrogen sulfide.

5. Toxins and Antigenic Structure of Clostridia. Pathogenicity of *Clostridia* is primarily associated with the elaboration of toxins. With certain important exceptions, the toxins are species specific. In sharp contrast most species exhibit a heterogeneous antigenic structure of the cells. This is made very clear in McCoy and McClung's (1938)[50] review. The heterogeneous character is evident in agglutination, precipitin and complement-fixation reaction. Little is known of the carbohydrate content of the cells. Meisel (1936)[57] isolated a polysaccharide from "*B. amylobacter*" and Jaminez (1931) and Reed and Orr (1940)[75a] have made similar isolations from *C. welchii* but the compounds proved to be nonspecific.

C. welchii Toxin. Bull and Pritchett (1917)[10] demonstrated soluble toxin in filtrates of *C. welchii* of human origin and from it prepared an antitoxin. This toxin they found contained two elements, a *hæmotoxin* and a lethal toxin which Henry called *myotoxin.* Much subsequent work appeared to indicate that all toxigenic strains of *C. welchii*, Henry (1920),[33] Reed, Orr and Campbell (1927), produced identical toxins as demonstrated by antitoxin neutralization.

Subsequently considerable controversy arose, which is still unsettled, concerning the relationship of *C. welchii* to flatulent diarrhea,[60] and toxemia of intestinal obstruction in man.[55] Also a group of organisms have been isolated from enterotoxemias, particularly of sheep, which closely resemble or are indistinguishable from the classical *C. welchii* of Welch and Nuttall except in the specificity of their toxins. The first of these was isolated by Gaiger and Dalling (1923),[23] Mason (1935),[48] sometimes called *Bacillus agni.* McEwen (1929)[51] then isolated a similar organism, *B. plaudis*, from *struck* disease of sheep. A third organism isolated from *pulpy kidney* of sheep by Bennetts (1932)[4] and later from other herbivorous animals has been called *B. oritoxicus.* Wilsdon (1931)[103] classified these 4 organisms, on the basis of toxin neutralization, as *C. welchii* types A, B, C and D. The toxins and antitoxins display considerable overlapping of factors.[24,72] The present position may be summarized as follows:

Species	Type (Wilsdon)	Toxins produced (Glenny)
C. welchii (Welch and Nuttall)[102]	A	α, ζ
B. agni (Dalling)	B	α, β, ε, traces γ, ζ
B. plaudis (McEwen)[51]	C	α, β, γ, traces δ
B. oritoxicus (Bennetts)[4]	D	α, ε

The properties of these toxins in physiologic terms are: α, hemolytic, lethal, necrotic; β, lethal, necrotic; γ, lethal; δ, hemolytic; ε, lethal, necrotic; ζ, lethal.

So far only the A type, the classical *C. welchii* of Welch and Nuttall, has been isolated from gas gangrene of man or from the human intestine,[6,7] though as stressed by the latter authors, there appears to be ample opportunity for human infections with the animal types.

Early work on the production of *C. welchii* toxin[33,97a] involved cultivation in a complex meat infusion medium. MacFarlane and Knight (1941),[45] working with Type A, simplified the medium and greatly increased the yield of α toxin.

The older methods of assaying α toxin consisted in determinations of lethal effects by intravenous injection generally in mice, *in vitro* determination of hemolysis and necrotic effects by intradermal injection.[46] Nagler (1939)[59] observed a specific reaction between α toxin and normal human serum. When the two are mixed an opalescence occurs. MacFarlane *et al.* (1941)[46] have since shown a similar reaction to occur when toxin is mixed with the crude lecitho-vitellin solution obtained from egg yolk. Van Heynigen (1941)[96] has improved the quantitative features by estimating the toxin on the basis of the amount of turbidity produced and MacFarlane and Knight have shown a parallelism between toxicity, turbidity of egg yolk solution and lecithinase activity.

It remains to be demonstrated how satisfactory this α toxin produced on MacFarlane and Knight's type of medium and determined by lecithinase activity may be in the production of *C. welchii* toxin and antitoxin but it appears to have made possible the efficient production of these agents.

C. welchii Antigens.   Little work has been done on the antigenic differentiation of A, B, C and D types beyond the specificity of toxins but among A types it has so far been impossible to establish antigenic relationship. Most reports based on agglutination reactions have indicated complete antigenic heterogenicity. Meisel (1936)[57] did find 6 of 10 Type A cultures belonged to one serologic group, but Reed and Orr (1940)[75a] found that of 85 Type A cultures, 6 showed close antigenic relationship on the basis of agglutination and precipitin reactions; a few others show overlapping of antigenic components and the balance show no antigenic relationship. Similarly Henderson (1940)[31d] found the O antigen of Type A to be strictly strain specific.

C. septicum Toxin.   This species produces a monotypic toxin notwithstanding somatic antigenic differences, Robertson (1919–20),[80] Bengston (1933, 1934),[3] Pasternack and Bengston (1936)[67] have shown that the rapid killing on intravenous injection of the toxin is due to a specific toxin on heart muscle. Walbum and Reymann (1936)[97b,c] have obtained good yields of toxin on an infusion-peptone medium.

C. septicum Antigen.   Felix and Robertson (1928)[19] indicated an H and O antigen in this species. They originally distinguished 4 types on the basis of H agglutinins and later Davesne (1928)[16] recognized 6 types. Bengston (1933),[3] however, could only identify 4 types. The several H antigenic types, Felix and Robertson (1928)[19] found to possess closely related O antigens and Henderson (1934, 1935)[32] found the O antigens of Types II and IV to be identical and distinguishable from those of Types III and I.

The O antigens of this species have a further interest. Robertson and Felix (1930)[81] claimed type specific protective value of O immune serum. Though questioned by Weinberg, Davesne and Haber (1932),[100] Robertson and Felix's[81] results have been confirmed by Henderson (1934, 1935).[31c.?] These considerations should be kept in mind in connection with the use of antitoxic sera.

C. novyi. Walbum and Reymann (1937)[97d] have obtained good yields of a specific toxin on an infusion-peptone medium.

It is impossible to come to any conclusion at this time concerning the identity of some 3 or 4 variously described "species," largely on account of conflicting reports of toxin specificity. *C. novyi* is generally regarded as synonymous with *C. œdematiens* of Weinberg and Séguin.[98] But Weinberg, Nativelle and Prévot (1939)[101] find antisera will neutralize toxin from all strains of *C. œdematiens* but not toxins of *C. novyi.* They also find that "*Bacillus bellonensis*" of Sacquépée (1916)[84] produces a specific toxin. They therefore consider the three to be valid species.

C. sordellii, C. bifermentans, C. œdematoides. There has been much difference of opinion as to the identity of these three problematical species. *C. sordellii,* described by Sordelli (1923)[88] and Hall and Scott (1931),[28] and *C. œdematoides,* described by Meleney *et al.* (1927),[58] were shown by Hall (1929)[26] to give cross-agglutination reactions as well as identical biochemical reactions. The latter author therefore suggested that they were identical and on the basis of priority proposed the name *C. sordellii.*

Later Clark and Hall (1937)[14] found cross-agglutination reactions with *C. bifermentans* and Stewart (1938)[92a] found *C. bifermentans* antiserum protected against *C. sordellii* toxin.

C. sporogenes. Hall and Stark (1923)[27] claimed some degree of homogenicity of all strains on the basis of agglutination, but Zeissler and Rossfield (1928)[105] recognized three groups. On the other hand, McClung (1937)[49a] and Smith (1937)[85] found some antigenic relationship with *C. parabotulinum* and *C. histolyticum.*

Other Species of Clostridium. Agglutination studies on several other pathogenic species have been of value in establishing identity: *C. paraputrificum* and *C. capitovalis,*[86a,87] *C. difficile,*[86b] *C. carnis* and *C. fallax.*[18]

6. Factors Which Influence Infection by Clostridia. The more important gas gangrene species are widely distributed in soils and animal feces. Zeissler and Neller (1927)[104] found the following distribution in 200 European soil samples: *C. welchii* present in 100%, *C. novyi* 45%, *C. septicum* 8%, *C. histolyticum* 2%.

This wide distribution, together with the fact that pathogenic *Clostridia* are frequently found in wound exudates where there is no evidence of *Clostridial* infection, raises the question of factors which permit or promote the development of infection. Fildes (1927, 1929)[20b,c] has shown that in the case of *C. tetani* spores will germinate in the tissues only when the surrounding fluid is poised at an Eh of +0.01 volts or more negative oxidation-reduction potential. Plotz and Geloso (1930)[70] extended these observations. We know that *C. welchii* and certain other species of the gas gangrene group will germinate and grow at a less negative O/R potential. However, this appears to be the most important factor in the development of *Clostridial* infections.

Several simple circumstances contribute to the production of favorable oxidation-reduction potentials in wounds. These may be summarized as: deep wounds in which air is excluded, the presence of devitalized tissue, toxic substances, foreign bodies, bacterial toxins. Dead or partially devitalized tissue, especially muscle, from which air is excluded, tends to assume a reducing potential. Certain substances, which may be introduced into a wound, as calcium salts, foreign bodies as cloth or soil, tend to promote necrosis and a reducing potential. It is obvious that a single spore or group of spores may be enclosed in microscopic masses of necrotic material which, with the exclusion of air or circulating blood, may become

sufficiently reducing to permit germination. Once germination and growth of a toxin forming species has occurred the accumulation of toxin will promote necrosis, reducing potentials, and thereby the spread of infection. On the other hand it has been shown by several authors,[11,17,95] that spores or even active vegetative organisms of several species of the gas gangrene group may be injected intramuscularly into animals without producing more than a slight transient reaction. Turner's results suggest, moreover, that spores which have been injected into tissues or introduced into wounds where they fail to germinate may develop at a considerably later data following injury or an unrelated infection which provides the necessary conditions for anaërobic growth.

In the production of experimental gas gangrene in guinea pigs, Reed and Orr (1942)[75b] found the following procedure the most efficient of several procedures tested: a wound was made deep into the thigh musculature, a fragment of excised muscle was placed in the lumen of the wound, 0.1 gm. of finely divided *sterile* soil and 1 drop of a 1 to 10,000 dilution of a young broth culture of the organism was added. The wound was then tightly closed with two rows of continuous sutures, one in the muscle, one in the skin.

Once spore germination has occurred and a local infection become established, extension of the infection is ordinarily rapid. It may remain localized in the wound, spread into a single muscle or group of muscles, spread into an entire segment of a limb or in the fulminating type there may be a general spread in all directions. The most important factors in the spread are fibrinolytic enzyme,[76] and toxin produced by the organisms.

Kropp and Smith (1941)[41] have shown that the earliest and most pronounced effect of the infection is to be seen in the connective tissue of the wound. Rapidly spreading edema appeared, involving first the subcutaneous connective tissue and a little later connective tissue of muscle bundles. Within 5 hours, in the case of *C. welchii* wound infections in guinea pigs, collagen fibers are swollen and fragmented and the cellular elements of the connective tissue largely broken down. This is to be seen not only where organisms were proliferating but beyond the margins where organisms are not detectable. At this stage and for some hours, connective tissue destruction with healthy skeletal muscle adjacent to it is the rule. There is no indication of muscle destruction in the absence of at least partial destruction of adjacent connective tissue. Gas spaces are early apparent as an accompaniment of edema. Blood-vessels of the connective tissue and muscle are thrombosed and frequently the endothelium of their walls rupture. Later destruction of muscle occurs and the infection appears to spread in the muscle. As the muscle is invaded, organisms make their way from the wound toward its extremities until it is totally destroyed. Frequently distinct zones appear. At the actual wound the muscle may be black, friable and diffluent, succeeded by a deep red zone and sometimes a yellow band appears adjacent to a healthy portion. Gas can be demonstrated, first as bubbles between the muscle fibers and later in the surrounding areolar tissue.

Physical signs. These differ widely. In a strictly localized gas gangrene infection the only sign may be a foul-smelling discharge containing gas bubbles. As the infection spreads, swelling of the part appears and yields a tympanic note on percussion. At a further stage the swelling increases, the skin acquires a dusky hue and tympanitis and crepitation become more marked. Still later the skin shows mottling with purple patches and finally becomes greenish yellow. At times, however, the gangrene of deep muscle may be far advanced though covered by apparently normal skin.

Pathologic Anatomy. Details of the late pathologic changes are adequately described by Kettle (British Committee Report on Anaërobic Infection, 1919), Eliot (Medical Department of the U. S. Army in the World War, Vol. XI, 1927) and others.

Physical signs and gross pathology of infection by the different gas gangrene species of *Clostridium* do not differ very widely. In the case of infections with *C. septicum* or *C. novyi* there tends to be a more copious accumulation of mucoid material in the subcutaneous spaces and between muscles than in the case of *C. welchii* infections. In the former this material is more deeply blood stained and the skin ordinarily appears more deeply discolored. In the case of *C. sordellii* infections of animals the appearance is more like that of *C. septicum* or *C. novyi* than *C. welchii*. Where wound infections are complicated by the presence of proteolytic species, especially *C. ...., C. ...raputrificum* or *C. histolyticum* the exudates tend to be .... and the local tissues of the infected wound tend to undergo slightly more rapid destruction.

7. Treatment of Gas Gangrene. (*a*) *Toxoids.* In a previous section, knowledge of toxin production by the principal gas gangrene species was reviewed. *C. welchii* toxoid has been prepared by Penfold and Tolhurst (1937, 1941),[69a,b] Plummer (1939)[71] and Stewart (1940, 1942).[92b,c] The latter author has shown that *C. welchii* toxins may be detoxified with 0.3% formalin, concentrated by ammonium sulfate precipitation and finally precipitated with alum. Guinea pigs with circulating antitoxin, as a result of immunization with this toxoid, are protected against many lethal doses of *C. welchii* toxin or culture.

C. novyi and *C. septicum* toxoids have been prepared by Weinberg and Barotte (1929)[99] and other work is now in progress in several laboratories on the more efficient production of these toxoids. As indicated in the earlier section on toxin production this will probably be successful.

It has been suggested that *C. welchii* toxoid, which is now available or could readily be made available in quantity, should be used in the army as a prophylactic measure. And, if and when *C. septicum* and *C. novyi* toxoids become available they should be combined with that of *C. welchii*. It is probable that these toxoids could be combined with T. A. B. vaccine—tetanus toxoid.

In these considerations for the future it must be remembered that gas gangrene is both a toxigenic and highly invasive infection. It is quite possible that active antitoxin immunity will prove to be inadequate.

(*b*) *Antitoxin.* Reports of the use of gas gangrene antitoxin either prophylactically or therapeutically are conflicting. The best of the last war reports are from Weinberg and Séguin (1918).[98] Of 50 wounded, treated with a polyvalent *C. welchii, C. septicum, C. novyi* serum 5 to 18 hours after injury, 25 died within a day without showing gas gangrene; the remainder recovered without developing gangrene. If these cases had followed the general average, 1 to 6 should have developed the disease. Of 30 patients with developed gas gangrene who were given polyvalent serum, 19 recovered. At the same time, of 66 gas gangrene patients who were given no serum 35 died. Newell (1939)[61] has advocated the early intravenous use of large doses of polyvalent antitoxin.

Gordon and McLeod (1941)[24a] have recently shown that specific antitoxic sera give good results in experimental *C. welchii, C. septicum* or *C. novyi* gas gangrene in guinea pigs.

The best method of preparing antiserum is still in question. Antitoxic serum prepared in horses by immunization first with formalized then with

pure toxin has given good results against experimental toxemia. But, as previously noted, Robertson and Felix (1930)[81] and Henderson (1934, 1935)[31b,c] have indicated that an antibacterial serum produced with the O antigen of *C. septicum* is superior to antitoxic serum in the prevention of this infection in experimental animals.

(c) *Roentgen Ray.* Kelly and Dowell (1936)[37] have advocated the use of Roentgen ray in treatment of gas gangrene. The results are far from convincing.

TABLE 4.—EFFECT OF SULFANILAMIDE AND TWO DERIVATIVES ON GUINEA PIGS INOCULATED WITH 10 MINIMUM LETHAL DOSES OF CL. WELCHII

| Number of animals | Medication, gm. | | Recovered, % | Died, % | Average survival time, hours |
	Locally in wound	Orally			
		Sulfanilamide			
23	Nil	Nil	0	100	25
15	Nil	0.1, twice daily	0	100	33
20	0.15	Nil	40	60	87
30	0.15	0.1, twice daily	42	58	103
		Sulfathiazole			
25	Nil	Nil	0	100	26
5	Nil	0.1, twice daily	60	40	100
61	0.15	Nil	97	3	169
5	0.15	0.1, twice daily	60	40	170
		Sulfadiazine			
5	Nil	Nil	0	100	14
10	0.15	Nil	80	20	80

TABLE 5.—EFFECT OF SULFANILAMIDE AND TWO DERIVATIVES ON GUINEA PIGS INOCULATED WITH 10 MINIMUM LETHAL DOSES OF CL. SEPTICUM

| Number of animals | Medication, gm. | | Recovered, % | Died, % | Average survival time, hours |
	Locally in wound	Orally			
		Sulfanilamide			
15	Nil	Nil	0	100	35
5	Nil	0.1, twice daily	0	100	72
8	0.15	Nil	25	75	84
5	0.15	0.1, twice daily	20	80	114
		Sulfathiazole			
15	Nil	Nil	0	100	37
5	Nil	0.1, twice daily	100	0	
15	0.15	Nil	87	13	222
5	0.15	0.1, twice daily	80	20	216
		Sulfadiazine			
5	Nil	Nil	0	100	31
10	0.15	Nil	100	0	

(d) *Chemotherapy.* Early work on chemotherapy of experimental gas gangrene in animals in which sulfonamides were administered orally gave indifferent results. Stephenson and Ross (1940).[91] Later experiments in which sulfonamides were given locally in the experimental infected wounds yielded highly successful results.[5,30,54,75b,d]

The results of one series of experiments[75d,e,f] are summarized in Tables 4 to 7. Results obtained by Hawking (1941),[30] McIntosh and Selbie (1941)[54] and Bliss, Long and Smith (1942)[5] are, in general terms, similar. These data are based on experiments in guinea pigs in which experimental wound infections were established by a method described in Section 6 of this paper. Where oral treatment was used the first dose was given 1 hour previous to wounding and continued, 2 doses per day, 0.1 gm. per dose in 300 gm. guinea pigs. In local treatment the drug, as a dry powder, was introduced at the time of infecting, a single dose of 0.15 gm. for 300 gm. guinea pigs, or at various intervals after infection.

In general it will be observed from Tables 4 to 7 that oral treatment

was definitely inferior to local wound treatment, although with the more efficient drugs, sulfathiazole and sulfadiazine, the contrast between local and oral treatment was not as great as with the less efficient sulfonamides.

As indicated in the tables, sulfanilamide was least efficient and sulfathiazole and sulfadiazine most efficient of those tested. Sulfapyridine, sulfamethylthiazole and sulfanilylguanidine (not shown in the tables) were intermediate in their action between sulfanilamide and sulfathiazole or sulfadiazine.

TABLE 6.—EFFECT OF SULFANILAMIDE AND TWO DERIVATIVES ON GUINEA PIGS INOCULATED WITH 10 MINIMUM LETHAL DOSES OF C. NOVYI

Number of animals	Medication, gm.		Recovered, %	Died, %	Average survival time, hours
	Locally in wound	Orally			
		Sulfanilamide			
15	Nil	Nil	0	100	35
18	Nil	0.1, twice daily	22	78	55
25	0.15	Nil	24	76	69
23	0.15	0.1, twice daily	22	78	97
		Sulfathiazole			
8	Nil	Nil	0	100	46
5	Nil	0.1, twice daily	100	0	
20	0.15	Nil	85	15	109
5	0.15	0.1, twice daily	80	20	162
		Sulfadiazine			
5	Nil	Nil	0	100	31
10	0.15	Nil	40	60	121

TABLE 7.—EFFECT OF SULFANILAMIDE AND TWO DERIVATIVES ON GUINEA PIGS INOCULATED WITH 10 MINIMUM LETHAL DOSES OF CL. SORDELLII

Number of animals	Medication, gm.		Recovered, %	Died, %	Average survival time, hours
	Locally in wound	Orally			
		Sulfanilamide			
11	Nil	Nil	0	100	32
5	Nil	0.1, twice daily	0	100	52
3	0.15	Nil	66	34	56
5	0.15	0.1, twice daily	40	60	82
		Sulfathiazole			
5	Nil	Nil	0	100	24
17	0.15	Nil	0	100	62
		Sulfadiazine			
5	Nil	Nil	0	100	21
10	0.15	Nil	0	100	65

Of the four most important gas gangrene species of *Clostridia* tested, it is apparent from the tables, *C. welchii* infections were most readily controlled; *C. septicum* and *C. novyi* less responsive but well controlled by sulfathiazole. *C. sordellii* infections were not significantly influenced by any chemotherapy tested. It has been previously noted, however, that *C. sordellii* is a relatively rare organism. In mixed infections or where one or more of *C. welchii*, *C. septicum* or *C. novyi* was introduced along with *C. sporogenes* or *C. histolyticum*, chemotherapy was as effective as against a single infecting organism.

When gas gangrene infections were permitted to become well established in the animals before chemotherapy was started, results were inferior or negative. In experimental animals where fatal infections developed in an average of 25 to 35 hours, a delay of 3 hours in initiating local treatment had no significant influence on the effects of chemotherapy. A delay of 5 to 6 hours, when infection was established and extended well beyond the local site of the wound, chemotherapy proved to be only slightly effective. Longer delay rendered the chemotherapy useless.

The advantage of local over oral administration appears to be largely a matter of local concentration in the infected or potentially infected tissues. Reed and Orr (1941)[75b,c] have shown (Fig. 1) that when sulfanilamide or sulfathiazole are introduced into experimental wounds the concentration of drug in the musculature of the wounded leg is much higher than in the blood stream. In contrast when the drug is administered orally the concentration is the same in all tissues as is to be expected from the results of Marshall, Emerson and Cutting (1937).[47]
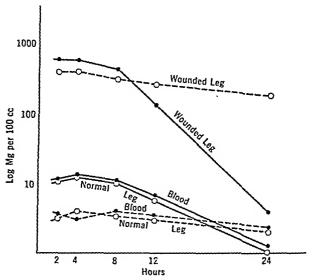
FIG. 1.—Changes in concentration of sulfanilamide (solid lines) and sulfathiazole (broken lines) in blood, normal muscle of leg and wounded muscle of leg following a single 0.15 gm. dose applied locally in the wound.

The large concentration of sulfonamides in wounds does not appear to impede healing.[36] Reed, Orr and Anderson (1942)[77] have shown that sulfathiazole up to 80 mg. per 100 cc. in serum does not retard the growth of fibroblasts in tissue cultures. In higher concentrations growth of fibroblasts is inhibited but if after several days' exposure to saturated solutions of sulfathiazole the cells are transferred to normal serum characteristic growth occurs. Reed and Orr (1942)[75c] have also shown that polymorphonuclear leukocytes are able to phagocytose staphylococcus at a normal rate in the presence of concentrations of sulfathiazole up to 80 mg. per 100 cc. Kropp and Smith (1941)[31] found that in experimental gangrene in guinea pigs treated locally with 0.15 gm. of sulfathiazole there is a massing of leukocytes and small lymphocyte-like cells at the periphery of the wound or a few millimeters beyond it which began to appear a few hours after infection. This condition was absent in untreated animals. Macey (1941)[41] and Klepser and Veal (1942)[38] state that human skin grafts develop normally in the presence of large concentrations of sulfanilamide and some of its derivatives.

In applying these animal results to man it cannot be emphasized too strongly that they indicate chemotherapy to be a prophylactic and not a definitive treatment of gas gangrene. Sulfonamides should be applied as soon as possible after a wound has been inflicted, with the objective of

retarding a possible infection until circumstances permit proper surgical procedure. It is impossible to suggest time limits, as no two wounds are alike or receive similar inoculations, but it is evident that the drug must be introduced before there has been any extensive gas gangrene infection—this may be a matter of a few hours or it may be safely delayed for several hours.

Surgical treatment should be introduced regardless of how early the sulfonamide may have been introduced. As Fletcher and Raven (1940)[22] and Ogilvie (1940)[62] suggest, the surgery will depend upon the condition of the patient. The procedures include: complete excision of the wound with removal of foreign and injured or infected tissue. All muscle tissue showing departure from the normal should be excised. To accomplish this it may be necessary to excise a complete muscle from origin to insertion, or even to sacrifice a group of muscles. In the case of fulminating infection, amputation may be necessary. If chemotherapy is applied early and the drug well distributed in or over the wound area extensive infections should be rare.

When débridement is complete *sterile* sulfonamide may again be applied. Present knowledge suggests that sulfathiazole or sulfadiazine are the most valuable.

Many surgeons at the present time supplement local chemotherapy and débridement with the Orr-Trueta immobilization procedure.[94] The early Trueta procedure of immobilization without chemotherapy as a means of preventing the development of gas gangrene has been questioned by many bacteriologists. In experimentally infected animals it has proven to be a failue.[75f]

(c) *Combined Chemotherapy and Serum Treatment.* There is nothing to contraindicate the combination of these two forms of therapy. Henderson and Gorer (1940)[32] have shown that in the case of *C. septicum* in experimental animals, sulfapyridine and antibacterial serum are more effective than either drug or serum alone. Reed and Orr (1942)[75d] have shown, in a small group of animals infected with *C. sordellii* that a combination of sulfathiazole and specific antitoxin resulted in recovery, whereas either treatment alone had no significant influence on the infection.

APPENDIX
MEDIA FOR CLOSTRIDIA

The following media were suggested by Reed and Orr (1941)[75c] for the isolation and identification of gas gangrene *Clostridia.*

1. *Plating Media, Surface Colonies.* (a) Blood agar is satisfactory for most purposes and has the added advantage of differential hemolytic reactions. (b) Clear plating media has certain advantages in the differentiation of colony types. Two formulæ have given equally good results:

A. Brewer's sugar-free broth, desiccated . . . . . 62.5 gm.
   Dextrose . . . . 1 gm.
   Agar . . . . 20 gm.
   Water . . . . 1000 ml.
   Adjust to pH 7.6

B. Proteose peptone . . . . 20 gm.
   Na₂HPO₄ . . . . 2 gm.
   Dextrose . . . . 1 gm.
   Sodium thioglycolate . . . . 1 gm.
   Agar . . . . 20 gm.
   Water . . . . 1000 ml.
   Adjust to pH 7.6

2. *Plating Media, Subsurface Colonies.* For subsurface colonies either *A* or *B*, above, with 7.5 gm. of agar to the liter have been satisfactory. This is the procedure of Greenberg (1941)[25] except that he used test tubes, whereas we prefer to use plates in anaërobic jars.

3. *Fluid Media for Biochemical Reactions.* (a) *Milk:* Of several preparations tested, the most satisfactory has resulted from following the suggestion of Hastings and McCoy (1932)[29] to add "reduced iron." More uniform results have been obtained with dried skim milk than with fresh milk. Bacto dried milk and a commercial Canadian product, milkite, have proved equally suitable. One hundred grams of dry milk is mixed with 1000 cc. of cold water, strained through gauze, adjusted to pH 6.8 (more alkaline milk darkens on autoclaving) and dispensed to tubes to which 0.05 to 0.1 gm. of reduced iron (Merck's "reduced with hydrogen") had previously been added. In this medium 5 to 100 organisms provides a suitable inoculum. Stormy fermentation, when it occurs, is generally marked in less than 24 hours.

(b) *Sugar-free base for fermentations:*

Bactopeptone or proteose peptone	20 gm.
Sodium chloride	5 gm.
Sodium thioglycolate	1 gm.
Agar	1 gm.
Water	1000 cc.

For fermentation reactions the sugars should be sterilized by filtration and added to the sugar-free base after autoclaving. Bromthymol blue is a satisfactory indicator, but since it tends to be reduced during the growth of anaërobes it is added at the end of the growth period and the reactions are read at once. Cultures in the sugar-free base or with a non-fermentable sugar present remain on the alkaline side of this indicator. Fermentable sugars, without exception, are sufficiently broken down in less than 24 hours to give a frank acid reaction. Production of gas has not been considered, as some species produce it from peptones.

The most significant differences between the 20 odd species of gas gangrene bacilli are to be seen in their action on dextrose, lactose, maltose, salicin and sucrose.

(c) *Liquefaction of gelatin:* The best results have been obtained with the following formula:

Gelatin	50 gm.
Bactopeptone	10 gm.
Sodium phosphate (Na₂HPO₄)	2 gm.
Dextrose	1 gm.
Sodium thioglycolate	1 gm.
Water	1000 cc.

All species in the group grow rapidly in this medium. Those which liquefy gelatin within 10 days give an extensive or a complete reaction within 24 hours. This medium without peptone gives good results, but a few species, especially *C. tetani*, grow sparingly.

This is essentially the medium recently described for toxin production. As will be noted later, the same culture may be used to measure gelatin liquefaction and toxin production.

(d) *Production of hydrogen sulfide:* Most if not all species of gas gangrene organisms produce at least a trace of hydrogen sulfide if a suitable substrate is supplied and a sufficiently sensitive indicator is used. Media containing appreciable amounts of sodium thioglycolate, cystine, glutathione and probably other sulfhydril-containing compounds yield considerable hydrogen sulfide with all species tested. On the other hand, mediums containing 1% to 2% of peptone rich in organic sulfur, such as proteose peptone, and one of the usual forms of iron as an indicator show darkening with all species tested. Spray (1936)[36] apparently recognized these facts and developed a rather curious lead acetate medium, which we have been unable to reproduce with any uniformity.

Under these circumstances it seemed desirable to select a medium which will give a clear-cut positive reaction with a large to moderate yield of hydrogen sulfide

and would give a negative reaction with minute traces. Two media fulfill these specifications fairly satisfactorily, producing readable reactions in 24 hours or less which agree moderately well with the conflicting records concerning the several species.

A. Proteose peptone . . . . 20 gm.
   Sodium phosphate (Na₂HPO₄) . . . . 2 gm.
   Dextrose . . . . 1 gm.
   Agar . . . . 2 gm.
   Water . . . . 1000 cc.

Dissolve, adjust to pH 7.6 and add 10 cc. of 2% lead acetate. This results in a cloudy precipitate which, however, remains after autoclaving in reasonably stable suspension.

B. Modified from Hunter and Crecelius (1938).
   Proteose peptone . . . . 20 gm.
   Sodium phosphate (Na₂HPO₄) . . . . 2 gm.
   Agar . . . . 1 gm.
   Dextrose . . . . 1 gm.
   Water . . . . 1000 cc.

Dissolve, adjust to pH 7.6 and add 10 cc. of 1.5% bismuth and ammonium citrate. This ordinarily produces a solution which remains clear after autoclaving.

(e) *Formation of indol:* The sugar-free base (described under media for sugar fermentation) serves satisfactorily as a test medium for indol formation, but the following mixture gives more consistent results:

Bactotryptone . . . . 20 gm.
Sodium phosphate (Na₂HPO₄) . . . . 2 gm.
Dextrose . . . . 1 gm.
Agar . . . . 1 gm.
Sodium thioglycolate . . . . 1 gm.
Water . . . . 1000 cc.

All indol formers in the group give in this medium strongly positive reactions in 24 hours with Ehrlich's reagent.

It has been shown by Reed (1942)[78] that certain species which give negative reactions for indol do so because the indol is broken down as rapidly as formed. This is not considered in the tabular statements (Table 1). All species which give a negative reaction for indol are included among those which do not form indol.

(f) *Reduction of nitrate:* Cultures at 24 hours in the following medium give clear-cut reactions for nitrite with Tittsler's (1930)[93] sulfanilic acid, dimethyl-α-naphthylamine reagent:

Bactotryptone . . . . 20 gm.
Sodium phosphate (Na₂HPO₄) . . . . 2 gm.
Dextrose . . . . 1 gm.
Agar . . . . 1 gm.
Potassium nitrate . . . . 1 gm.
Water . . . . 1000 cc.

It has been shown by Reed (1942)[78] that certain species of *Clostridium* fail to reduce nitrates; others reduce nitrates to nitrites, and still others reduce nitrites as formed to ammonia. In this paper, however, the former and the latter are grouped together, as has been done in the past, as species which fail to accumulate nitrites.

(g) *Decomposition of protein:* The active proteolytic species give readable reactions in 24 to 48 hours on a variety of media. Less active species give indefinite results for long periods. The most rapid results have been obtained with a medium consisting of equal parts of one of the plating media (described above) and skim milk, in plates. The milk is prepared as described in (a).

REFERENCES

(1.) Allyn, W. P., and Baldwin, I. L.: J. Bacteriol., 20, 417, 1930.
(2.) Bengston, I. A., J. Bacteriol., 25, 84, 1933. (3.) Bengston, I. A.: U. S. Pub. Health Rep., 49, 225, 1934. (4.) Bennetts, H. W.: Australian Inst. Sci. Ind. Bull., 57.

1, 1932.   (5.) Bliss, E., Long, P., and Smith, D. G.: War Med., 1, 799, 1941.   (6.) Borthwick, G. R., and Gray, J. D. A.: J. Exp. Path., 18, 119, 1937.   (7.) Bosworth, T. J.: Int. Soc. Microbiol., 2d Cong., p. 179, 1936.   (8.) Brewer, J. H.: J. Lab. and Clin. Med., 24, 1, 1939.   (9.) Brewer, J. H.: J. Am. Med. Assn., 225, 598, 1940.   (10.) Bull, C., and Pritchett, I.: J. Exp. Med., 26, 867, 1917.   (11.) Bullock, W., and Cramer, W.: Proc. Roy. Soc. London B, 90, 513, 1919.

(12.) Chalier, A., and Chalier, J.: La gangréne gazeuse, Paris, 1917.   (13.) Chauveau, A., and Arloing, S.: Bull. Acad. de méd., Paris, 13, 604, 1884.   (14.) Clark, F. E., and Hall, I. C.: J. Bacteriol., 33, 23, 1937.   (15.) Cramp, W.: Ann. Surg., 56, 544, 1912.

(16.) Davesne, J.: Compt. rend. Soc. de biol., Paris, 99, 763, 1928.   (17.) De Kruif, P., and Bollman, J.: J. Inf. Dis., 21, 588, 1917.   (18.) Duffett, N. D.: J. Bacteriol., 29, 573, 1935.

(19.) Felix, A., and Robertson, M.: Brit. J. Exp. Path., 9, 6, 1928.   (20.) Fildes, P.: (a) Sp. Rep. Ser. Med. Res. Council, London, No. 12, 1917; (b) Brit. J. Exp. Path., 8, 387, 1927; (c) Ibid., 10, 51, 1929.   (21.) Fildes, P., and McIntosh, J.: Brit. J. Exp. Path., 2, 153, 1921.   (22.) Fletcher and Raven, R. W.: War Wounds and Injuries, London, 1940.

(23.) Gaiger, S. H., and Dalling, T.: J. Comp. Path. Ther., 36, 120, 1923.   (24.) Glenny, A. T., Barr, M., Llewellyn-Jones, M., Dalling, T., and Ross, H. E.: J. Path. and Bact., 37, 53, 1933.   (24a.) Gordon, J., and McLeod, J. W.: Lancet, i, 407, 1941.   (25.) Greenberg, L.: Canadian Pub. Health J., 32, 84, 1941.

(26.) Hall, I. C.: J. Inf. Dis., 45, 159, 1929.   (27.) Hall, I. C., and Stark, N.: J. Inf. Dis., 33, 240, 1923.   (28.) Hall, I. C., and Scott, A. L.: J. Bacteriol., 22, 375, 1931.   (29.) Hastings, E. G., and McCoy, E.: J. Bacteriol., 23, 54, 1932.   (30.) Hawking, F.: Brit. Med. J., 1, 263, 1941.   (31.) Henderson, D. W.: (a) Brit. J. Exp. Path., 13, 421, 1932; (b) Ibid., 13, 166, 1934; (c) Ibid., 16, 393, 1935; (d) J. Hyg., Cambridge, 40, 501, 1940.   (32.) Henderson, D. W., and Gorer, P. A.: J. Hyg., Cambridge, 40, 345, 1940.   (33.) Henry, H.: J. Path. and Bact., 25, 1, 1922.   (34.) Hoogerheide, J. C.: J. Bacteriol., 34, 387, 1937.   (35.) Hunter, C. A., and Crecelius, H. G.: J. Bacteriol., 35, 261, 1938.   (36.) Jacoby, F., Medawar, P. B., and Willner, E. N.: Brit. Med. J., 2, 149, 1941.   (36a.) Kellett, C. E.: Ann. Med. Hist., 1, 452, 1939.   (37.) Kelly, J. F., and Dowell, D. A.: J. Am. Med. Assn., 107, 1114, 1936.   (38.) Klepser, R. G., and Veal, J. R.: J. Bacteriol., 43, 72, 1942.   (39.) Klinger, I. J., and Guggenheim, K.: J. Bacteriol., 35, 141, 1935.   (40.) Koch, R.: Mitt. a. d. k. Gesundheit., 1, 49, 1881.   (41.) Kropp, B., and Smith, D. G.: War Med., 1, 682, 1941.

(42.) Lepper, E., and Martin, C. J.: Brit. J. Exp. Path., 10, 327, 1929.   (43.) Lichstein, H. C., and Snyder, M. L.: J. Bacteriol., 42, 653, 1941.

(44.) Macey, H. R.: Proc. Staff Meet. Mayo Clin., 16, 758, 1941.   (45.) MacFarlane, M. G., and Knight, B. C. J. G.: Biochem. J., 35, 884, 1941.   (46.) MacFarlane, M. G., Oakley, C. L., and Anderson, C. G.: J. Path. and Bact., 52, 99, 1941.   (47.) Marshall, E. K., Emerson, K., and Cutting, W. C.: J. Pharmacol. and Exp. Ther., 61, 196, 1937.   (48.) Mason, J. H.: J. Vet. Sci. Anim. Ind., 5, 391, 1935.   (49.) McClung, L. S.: (a) J. Inf. Dis., 60, 122, 1937; (b) J. Bacteriol., 40, 645, 1940.   (50.) McCoy, E., and McClung, L. S.: Bacteriol. Rev., 2, 47, 1938.   (51.) McEwen, A. D.: J. Comp. Path. Ther., 43, 1, 1929.   (52.) McGaughey, C. A.: J. Path. and Bact., 37, 263, 1933.   (53.) McIntosh, J., and Fildes, P.: Lancet, 1, 768, 1916.   (54.) McIntosh, J., and Selbie, F. R.: Lancet, 1, 240, 1941.   (55.) McIver, M. A., White, J. C., and Lawson, G. M.: Ann. Surg., 89, 647, 1929.   (55.) Medical Research Committee Report on Anaërobic Infection of Wounds, London, 1919.   (57.) Meisel, H.: Compt. rend. Soc. biol., Paris, 123, 173, 1936.   (58.) Meleney, F., Humphreys, F., and Carp, L.: Proc. Soc. Exp. Biol. and Med., 24, 675, 1927; Surg., Gynec. and Obst., 45, 775, 1927.

(59.) Nagler, E. P. O.: Brit. J. Exp. Path., 20, 473, 1939.   (60.) Nelson, C. I.: J. Inf. Dis., 52, 89, 1933.   (61.) Newell, E. D.: Ann. Surg., 110, 100, 1939.

(62.) Ogilvie, W. H.: Wound Infections, London, 1940.   (63.) Orr, J. H., Campbell, W. A., and Reed, G. B.: Canadian J. Res., 2, 91, 1930.   (64.) Orr, J. H., Josephson, J., Baker, M. C., and Reed, G. B.: Canadian J. Res., 9, 350, 1933.   (65.) Orr, J. H., and Reed, G. B., J. Bacteriol., 25, 96, 1933.

(66.) Pacheco, G., and Costa, G. A.: Mém. de Inst. Oswaldo Cruz, 35, 381, 1940.   (67.) Pasterneck, J. C., and Bengston, I. A.: U. S. Pub. Health Ser. Bull., 163, 1, 1920.   (68.) Pasteur, L., and Jobert, C.: Compt. rend. Acad. d. sc., 85, 101, 1877.   (69.) Penfold, W. J., and Tolhurst, J. C.: (a) Med. J. Australia, 1, 952, 1937; (b) J. Path. and Bact., 52, 157, 1941.   (70.) Plotz, H., and Geloso, J.: Ann. Inst. Pasteur, 45, 613, 1930.   (71.) Plummer, H.: Canadian Pub. Health J., 39, 27, 1930.   (72.) Prigge, R.: Ztschr. f. Immunol., 89, 477, 1936.

(73.) Quastel, J. H., and Stephenson, M.: Biochem. J., 20, 1125, 1926.

(74.) Reed, G. B.: J. Inf. Dis., 45, 247, 1929.   (75.) Reed, G. B., and Orr, J. H.: (a) J. Bacteriol., 49, 411, 1940; (b) Lancet, 1, 367, 1941; (c) War Med., 1, 493, 1941.

(d) Ibid., 2, 59, 1942; (e) Ibid., 2, 639, 1942; (f) Ibid., 2, 83, 1942; (g) J. Bacteriol., 1943 (in press). (76.) Reed, G. B., Orr, J. H., and Smith, D.: Paoc. Soc. Exp. Bjol. and Med., 47, 228, 1941. (77.) Reed, G. B., Orr, J. H., and Anderson, R.: War Med., 2, 635, 1942. (78.) Reed, R. W.: J. Bacteriol., 44, 425, 1942. (79.) Roberts, R. S.: J. Comp. Path. Ther., 44, 246, 1932. (80.) Robertson, M.: J. Path. and Bact., 23, 153, 1919-20. (81.) Robertson, M., and Felix, A.: J. Exp. Path., 11, 14, 1930. (82.) Rosenthal, L.: J. Bacteriol., 34, 317, 1937. (83.) Rumpel, K.: Veröffentl. a. d. Geb. d. Mil.-Sanit., Berlin, 1918.

(84.) Sacquépée, E.: Compt. rend. Soc. de biol., Paris, 79, 115, 1916. (85.) Smith, L.: J. Bacteriol., 34, 409, 1937. (86.) Snyder, M. L.: (a) J. Bacteriol., 32, 401, 411, 1936; (b) J. Inf. Dis., 60, 223, 1937. (87.) Snyder, M. L., and Hall, I. C.: Zentralbl. f. Bakt. u. Parasitol., Abt. Orig., 135, 290, 1936. (88.) Sordelli, A.: Compt. rend. Soc. de biol., Paris, 89, 53, 1923. (89.) Sordelli, A., and Ferrari, J.: Compt. rend. Soc. de biol., Paris, 105, 245, 1930. (90.) Spray, R. S.: (a) J. Bacteriol., 25, 51, 1933; (b) Ibid., 32, 135, 1936. (91.) Stephenson, D., and Ross, H. E.: Brit. Med. J., 1, 471, 1940. (92.) Stewart, S. E.: (a) J. Bacteriol., 35, 13, 1938; (b) U. S. Pub. Health Rep., 55, 753, 1940; (c) War Med., 2, 87, 1942.

(93.) Tittsler, R. P.: J. Bacteriol., 19, 261, 1930. (94.) Trueta, J.: The Treatment of War Wounds and Fractures, New York, 1940. (95.) Turner, A.: Compt. rend. Soc. de biol., Paris, 98, 558, 1928.

(96.) van Haynigen, W. E.: Biochem. J., 35, 1246, 1247, 1941.

(97.) Walbum, L. E., and Reymann, G. C.: (a) J. Path. and Bact., 36, 469, 1933; (b) League of Nations Health Organ, Quart. Bull. (5) Spec. No. 690, 1936; (c) J. Path. and Bact., 42, 351, 1936; (d) Ibid., 44, 379, 1937. (98.) Weinberg, M., and Séguin, P.: La gangrène gazeuse, Paris, 1918. (99.) Weinberg, M., and Barotte, J.: Ann. de l'Inst. Pasteur, 43, 452, 1929. (100.) Weinberg, M., Davesne, J., and Haber, P.: Ann. de l'Inst. Pasteur, 49, 303, 1932. (101.) Weinberg, M., Nativelle, R., and Prévot, A. R.: Les microbes anaerobies, Paris, Masson et Cie, 1937. (102.) Welch, W., and Nuttal, G.: Bull. Johns Hopkins Hosp., 3, 81, 1892. (103.) Wilsdon, A. J.: Univ. Cambridge Inst. Anim. Path., 2d Rept., p. 53, 1931.

(104.) Zeissler, J., and Neller, K.: Arch. f. klin. Chir., 140, 153, 1927. (105.) Zeissler, J., and Rossfield, L.: Veröffentl. Krieg-und Konstitution path., 5, Heft 2, 1, 1928.

PREVENTIVE MEDICINE AND EPIDEMIOLOGY

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THE FUNCTIONS OF HYPOTHESES IN EPIDEMIOLOGY

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Many definitions of Epidemiology found in medical literature or heard in discussions of the subject tend to restrict this field of medical science to the use of particular methods, or to reflect some particular kind of disease problem under study. Others, such as the statement that epidemiology is the natural history of the disease, are so general that they fail to define just what is involved.

Recently, the editorial question in the *"American Journal of Public Health,"*[1] "What and who is an epidemiologist?" called forth a running stream of definitions. Most of these were busied with demands for partic-

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ular personalities, qualifications, skills or techniques, for establishing facts in one situation or another, or in one disease or another. All in all, they had the effect of limiting epidemiology to the doings of a few rare individuals and using relatively few special skills, rather than leaving elbow room for the pursuit of the real objective in whatever manner, or by whoever may be suited for the purpose.

Rather than Who is an epidemiologist? we should ask What is epidemiology?* One says it is the investigation of the extent, source and control of an *epidemic*, another, that it is the study of *past* epidemics. Some define it as the *statistical* study of disease. Still others set it up not as a science, but as a sort of mystery to be unraveled, either by the gumshoe or shoe leather method.[1] But John Bard in 1749, before the Weekly Society of Gentlemen of New York said, "Of all the subjects on physical knowledge there are none so amazing or which afford more useful speculation than the history of epidemical diseases. By epidemical diseases are meant general or spreading disorders attacking great numbers within the circle of its appearance at or near the same time;—proceeding from the contagious affection of the air and sometimes propagated by a contagion received from one, to another person unaffected."[3] Nearly 200 years later Frost said, "Epidemiology is something more than the total of its established facts. It includes their orderly arrangement into chains of inference which extend more or less beyond the bounds of direct observation." This modern version of Bard's "useful speculation" is probably most important of all, for the very magnitude of the phenomenon under study is reason for extending beyond the bounds of direct observation. Epidemiology is an attempt to understand disease, not so much as it affects the individual or as it behaves at a given time or place under the eye of the observer, but rather as it imposes itself upon whole groups of people without limits of size, time or space. The circumstances falling between cases may be of more significance than the cases themselves. In clinical medicine, the case begins with the onset of sickness, and terminates when the patient is feeling well again; but in epidemiology, the case begins when the patient is infected, and lasts as long as he is infective. In certain diseases the two may closely coincide, but in many, they may be widely or even totally divergent, for in certain diseases, even the majority of infected and infective individuals never have any sickness at all. In others, infectiousness may precede or long outlast the clinical disease. Thus, for epidemiologic purposes, the silent periods—the incubation period, infectious period or healthy carriage—may be even more important than the manifest illness. Again, many of the features of disease movement in a population are not amenable to direct observation, and even if they are, it is only on small samples from which inferences must be drawn in regard to the whole.

Disease can be seen when and where it occurs, but its infectious agent cannot be seen when it is spreading. For this reason, epidemiology to a considerable extent has been the formation of inferences in regard to how infectious agents spread from the distribution of disease which results from it. Time and place relationships between cases are the "established facts" which afford the basis for "chains of inference." Hirsch's *Historic and Geographic Pathology* in its time was epidemiology at its finest, for

* One is tempted to answer that epidemiology is "the study of epidemic disease," thus including all pertinent phases, descriptions, emphases, methods, subdivisions, philosophies, hypotheses, facts, modifying circumstances, and narrower concepts that improperly limit and confuse the answer.—Editor.

without the aid of the as yet unborn science of microbiology he pains-
takingly recorded the distribution of disease and drew inferences from it
as to *how* its microbic agent was spread. From the point of view of present
day knowledge, his inferences were often discrepant, but usually only
insofar as knowledge of the fields into which they lead were discrepant.
For example, his conclusion that malaria was due to "processes of decom-
position set up in organic matters" was right, broadly speaking, as far as
it could go in 1880. He correctly associated the disease with something
developing in water under particular conditions. Knowledge of just
what was brewing in the water had to wait advances in knowledge in the
field of "decomposition of organic matter" itself. But the conditions
defined by him under which malaria occurred might be recognized at
once in the light of present knowledge as those under which *Anopheles*
thrives.

However orderly such chains of inference may be, their correctness is
dependent in part on the weight of the circumstantial evidence on which
they are based, and in part on knowledge in the fields into which their
interpretations lead. As Frost well stated it, "The theories of epidemiology
which have been recorded at successive times have been limited in their
approach to present conceptions, not merely by the limits of the facts
known at the time, but equally or even more by the status of contemporary
knowledge and thought in other fields, since this has largely governed the
interpretations given to the facts."

The function of a hypothesis in epidemiology is therefore twofold:
(1) to arrive as near a conclusion as possible through preponderance of
circumstantial evidence; but, (2) perhaps more largely and equally impor-
tant, to form a plan or pattern to give direction to subsequent studies,
or to carry a question which has been raised in the course of studies in
one field of science across the boundary to other fields for further investi-
gation.

The ideal manner of progression in furthering knowledge would be to
form a hypothesis from initial studies to be borne out, amended, modified
or rejected in accordance with each additional investigation in the fields
into which it has led; and only when the sum total of the evidence has
become conclusive, to use the legal expression, beyond a reasonable doubt,
or the hypothesis has been thoroughly tested or suitably amended by tests
in other fields to allow it to be accepted as a conclusion or doctrine. An
example of this sort of sound hypothesis is seen in Hirsch's compilation of
data concerning the history and geography of malaria, culminating in the
statement that, "We shall not proceed far in explaining the endemicity
of the fever without the assumption of a material and specific poison, the
development of which depends on processes of decomposition of organic
matter under the conditions laid down in the 'swamp theory'."

How well Hirsch succeeded in establishing facts can best be shown by
the following quotations from his discussions. "Among the factors which
determine the occurrence and diffusion of the malarial diseases, climatic
and telluric conditions hold first place. The dependence of malaria pro-
duction on climatic influences, of which the geographic distribution over
the globe has already given us indications, is brought out in the most
definite way by the prevalence of malarial fever (1) at certain seasons, and
(2) under certain meteorologic conditions, particularly under the influence
of heat and atmospheric moisture. The question here raised leads us to
inquire into the influence on the production of malarial disease exerted
by those factors that are characteristic of the climate by conditions of heat

and moisture. That inquiry rests directly on our knowledge of the geographic distribution of malaria, and the facts given in the course of the foregoing sketch find a definite expression in the law that the disease shows a progressive decrease both in extent and intensity from the equator to the poles, and that there is a certain limit beyond which it does not occur either endemically or epidemically, or if it does occur, then only in cases imported.

"A rather high temperature, therefore—and all observers agree in this opinion—forms an essential condition for the development of malaria. A confirmation of this is found not only in the circumstance that the extent and intensity of the disease in malarious foci at the several seasons of the year are in direct proportion to the height of the respective temperatures, but also in the fact that the great epidemics or pandemics have been immediately preceded by hot years, or have coincided with them. But although there can be no reason to question the general importance of high temperature for the production of malaria, there is just as certainly another series of facts which serve to keep that significance within due limits.

"An influence not less pronounced than that of temperature is exerted by the degree of atmospheric moisture, or of the atmospheric precipitations that result therefrom. But inasmuch as this etiologic factor really deals with the saturation of the soil caused by the precipitations and with the fact that the saturation, when complete, sets limits to the development of malaria, then it is self-evident that we are concerned here with a certain measure, or with the relative amount of precipitation. The fall must be all the more copious, if it is to aid in the production of the disease, when the soil is naturally dry; while, on the other hand, a very heavy fall on a naturally wet soil will prevent the development of the disease till such time, at least, as the soil has again become in a measure dried through the evaporation or sinking down of the moisture within it. But there are still many unexplained exceptions to the rule which serve to show how far we are from having a complete insight into this factor, and it is only through careful analysis of the facts that we shall succeed in letting some light in upon the still very obscure region of etiology.

"The endemic and epidemic occurrence is affected by altitude and configuration of the ground under the general law that the extent and severity of malarial disease diminish in proportion as we ascend above sea level or as we move from level to hilly country. On the one hand, the mean summer temperature is a determining factor; the height to which malaria ascends is in definite ratio to the geographic position, and accordingly in an inverse ratio to the latitude of the place. The second factor in this relative immunity of elevated localities is undoubtedly the state of the soil as regards moisture, which is naturally different from the degree of moisture in the plain. Wherever malaria is endemic at more or less considerable elevations, the seat of the disease is always a valley with a small declivity or a basin-like depression in a plateau.

"An important aspect is undoubtedly that which presents itself in the question how far the disease depends upon the geological and physical conditions of the soil. Any evidence that the geological character of the soil itself is concerned is questionable and we may limit the influence of the soil to its physical characteristics—the porosity, degree of saturation, the amount of organic detritus, and further on the tillage, and perhaps also upon the products resulting from cultivation. The chief seat of malaria is always found where there is a permeable and highly hygro-

scopic clay soil, and least favorable of all is a sandy soil, readily open to saturation, but unable to retain the absorbed moisture, and becoming dry almost as soon as it is saturated. Under all these circumstances, then, the malaria-producing property of soil seems to depend on saturation of the ground.

"In the second place, we find malaria exceedingly common in small and often definitely circumscribed spots by the sides of lakes, small streams or brooks, pools, ponds and ditches (and extending just as far as the basin makes its influence felt in saturating the soil of the neighborhood).

"The amount of organic matter in the ground (or ground water) is the last of those properties of the soil which we have found to stand in relation to the origin of malaria."

And how well Hirsch fulfilled the second purpose of a hypothesis is shown by his statement pointing the finger of suspicion to a set of conditions now known to be those favorable to breeding of *Anopheles* mosquitoes. As he summarized it, "The close association of malaria with a particular kind of soil, highly saturated and rich in organic matter, and the fact that the disease breaks out whenever that kind of soil is subjected to a high temperature suggest the conclusion that the development of the morbid poison goes hand in hand with the processes of decomposition set up in organic matters under those circumstances."[6]

Particularly where these hypotheses are formed well in advance of developments in the specific fields into which they lead, they are likely to become less and less hypothesis and more and more doctrine or dogma. And, having become dogma, subsequent investigations are likely to take the form of attempts to support the hypothesis in favor; and we frequently witness amendments, modifications, or rejection of evidence (or its interpretation) when new evidence is not in line with the doctrine rather than a change in the hypothesis. Against the theory of the origin of pellagra from the consumption of decomposed maize, two important objections were encountered. But instead of bringing about a modification of the maize hypothesis—already become a doctrine—the conflicting observations themselves were ingeniously interpreted so as to be brought in line with the favored hypothesis. The first difficulty was the fact that maize is largely cultivated and used as a food in many areas in which pellagra was quite unknown. The proponents of the maize theory argued that in all these areas the corn was either thoroughly dried, thereby preventing decomposition; or the damaged maize was not eaten by man but made into food for the hogs. The second objection—the occurrence of sporadic pellagra which could in no way be associated with maize—was answered either by the assumption that other kinds of grain could under certain circumstances suffer changes like those of maize, or that such cases were so different, "not only in etiology but also in the nature and concatenation of the symptoms, that the judicial standpoint of all the more recent observers was that there never was more than a resemblance between them and the endemic disease. Arbitrarily made up groups of symptoms included nervous or psychical affections, with disorders of the digestive organs and with morbid appearances of the skin; and, after full collection and thorough scrutiny of all the observations relating to the matter, all recent observers found it necessary to speak of pseudo pellagra."[7]

But when the accumulation of evidence finally forces a change in hypothesis, the tendency has seemed to be not to amend or modify an existing hypothesis, but to launch a new one even in the face of large accumulations of evidence in favor of the older one. Perhaps one reason

why it is so easy to launch a new hypothesis is that an older one, however much soundness it may contain, not having afforded a practical solution of the disease problem, becomes wearisome and is easily set aside because of the hope offered by a new one. "It is not easy when divergent theories are presented to distinguish immediately between those which are sound and those which are merely plausible." (Frost.) And this has been especially true when epidemiologic inferences have led into fields not yet well bounded or cultivated. Favor veers from one to another with each new set of observations. Any former hypothesis in time comes to have its adherents, who continue to stress supporting evidence as well as inferences from favorable findings, remaining faithful to the old and rejecting the new. Meanwhile, the newly advanced hypothesis acquires followers—the more rapidly as it appears more promising—until, having gained enough to constitute "a strong minority," we witness the all too frequent situation of two opposed schools; each bending its efforts, not so much to the study of the problem as to the support of its own group, with one or the other gaining or losing with developments in one field or the other. And it is difficult, with the growth of opposing schools, even with acquisitions of knowledge, not to be swayed by preferences for one or the other existing doctrine, or to view both the opposed hypotheses dispassionately. Finally, and frequently because of the impetus of some particular development in knowledge, the more hopeful, newer hypothesis completely overthrows the older.

It frequently happens that, where there are two opposed concepts, it will be found that they were derived at different times under the influence of contemporary developments in one science or another; not so much from conflicting observations, as from resisting inferences evolved from essentially similar observations. And it is frequently the case that these resisting inferences were formed long in advance of developments in the specific fields involved. In the light of subsequent advances, it is seen that the approval of either concept necessitates the acceptance of assumptions of doubtful worth in the theory favored, and the rejection of valid evidence in the opposition.

Therefore, it is constructive to turn back to the data from which earlier concepts have been evolved in order to re-test them in the light of present knowledge, to seek out the discrepancies in each and the validities in both, which become more discernible with development of knowledge in the fields in which they lie. Thus, erroneously drawn propositions may be amended, or the validities in conflicting hypotheses which were formed from essentially the same type of observations may be proved adjustable into a different concept.

The changes which have taken place at different times in concepts of the epidemiology of leprosy well illustrate the manner in which hypotheses rapidly become doctrines, how new observations are rationalized to fit the favored dogma, and how older hypotheses are finally thrown over by newer and more hopeful ones. And, finally, it may be seen how by viewing the two hypotheses in leprosy, rejecting the assumptions of doubtful worth in both and accepting the validities in each, we arrive at a third hypothesis with which all the observations are in more perfect accord than with either of the two conflicting hypotheses.

The two opposed theories, contagion and heredity, have prevailed at different times in leprosy. These concepts were derived not so much from conflicting observations as from resisting inferences evolved from essentially similar observations. Both were formed long in advance of develop-

ments in the specific fields of science involved, and with acquisition of knowledge in these fields, discrepancies in each and validities in both become apparent. The approval of either concept necessitates the acceptance of assumptions of doubtful worth in the theory favored and the rejection of valid evidence in the opposition.

In the light of modern knowledge, it can now be seen that the familial tendency in leprosy upon which Danielson and Beck based their theory of heredity is not that of a hereditary disease—that is, it is not Mendelian; but, none the less, there is a striking familial tendency. It can likewise be seen that the long continued selectivity seen in family lines is not compatible with any known law of contagion, the theory which gained preference through the discovery of the Hansen bacillus. There is no longer any question as to the actuality of both familial tendency and contagion in leprosy. The validities as well as the discrepancies in both theories can best be harmonized by a third concept—that leprosy occurs as a result of contagion to be sure, but in the exposed who are hereditarily susceptible to the infection.[2]

In the earlier part of the nineteenth century, the formation of hypotheses from the facts relating to disease distribution was the only tool available to epidemiology. But this method yielded masterpieces of inference such as Budd in typhoid fever or Panum in measles. But in the latter part of the century, hypotheses lost ground and experimental proof was exacted. Finlay's long held *Stegomyia fasciata* hypothesis in yellow fever[5] was not established (he attempted experimental transmission) until, aided by Carter's demonstration of the extrinsic incubation period,[4] Reed was able to set up an appropriate transmission experiment with *Aëdes ægypti*.[9, 10]

Since epidemiology is so largely an inferential science, it is natural that hypotheses based on numbers of features or on a variety of findings, in other words on a preponderance of evidence, are more likely in general to point in the right direction than those based on some single feature. For example, the fallacy of the once common idea that seasonal prevalence of disease is necessarily an indication of mode of spread is now well known. The error in the generalization that diseases transmitted through upper respiratory contact are diseases of winter because of "crowding" and insect-borne or gastro-intestinal diseases necessarily occur in the opposite seasons because of summer increase in transmission, may be seen in the fact that no two of the upper respiratory diseases have the same seasonal curve. Diphtheria begins its increase in August, while whooping cough or meningococcus meningitis may remain epidemic well into summer. On the other hand, the insect-borne typhus (for obvious reasons, of course) is a disease of winter.

Perhaps it is because laboratory findings or experiments are in a sense more easily visualized than more or less laborious collections of data on disease distribution that some single experimental feature of disease so often takes preference in the formation of epidemiologic inferences over any amount of distributional evidence to the contrary. The older inference that hookworm infestation was due to drinking water,[7] based on the finding of hookworm eggs in the fecal discharges of patients could hardly have been made if the difference in incidence in those wearing shoes and those going barefooted had been considered.

The earlier history of the development of present day epidemiologic concepts is filled with erroneous hypotheses which have prevailed at one time or another. From the point of view of present day knowledge, it may be difficult to see how some of these could have evolved, until it is

remembered that in addition to reasons already stated—chiefly inadequate knowledge of fields into which the hypotheses lead, many of them were based on observations limited to the locality which could be covered by the single observer and without the aid of information concerning the behavior of the disease elsewhere. The first outbreak of poliomyelitis recorded in its epidemiologic aspects in this country was in Rutland County, Vermont, in 1894. The recorded outbreak extended only as far as Caverly could travel in a horse and buggy. Only recently this restricted occurrence was cited as having special epidemiologic significance, in spite of the fact that it is now well known that the outbreak was by no means confined to the area covered by Caverly's study. To be sure, there are local investigations which are classics in epidemiology—Budd on typhoid, and Snow on cholera—but more often, failure to view disease broadly has led to erroneous concepts. There are diseases which occur only in restricted areas, not because of any effort to keep them there, but because it is only in these areas that they find the necessary conditions for propagating themselves. For these, the cause is to be sought in local conditions. But for most, it is clear that disease in one people cannot be prevented, nor even understood, without taking into account its behavior in other places. We may still argue with Boswell and Johnson whether epidemic disease comes into St. Kildes on the wind, or on the ships which make the harbor with the favorable wind, but we know that epidemic disease, lurking in insects, goods and chiefly in the healthy carrier, recognizes no boundaries. In the past, distance itself aided in protecting one from the diseases of another. But the isolation of the past is a thing of the past, for microbes in their way enjoy the speed of modern travel as much as we do in our way. Thus the cause of most diseases is not local but is due to a condition or conditions in many areas. Study of the circumstances under which it travels or attention to conditions which can be associated with variations in its occurrence in different localities, may be more revealing than studies, however intensive, in one area.

The facts have sometimes been assembled by the traveling investigator, such as Panum in the Faroes; and Hansen, the Norwegian discoverer of the bacillus of leprosy, who in 1888 journeyed to Minnesota in the United States to investigate the disease in American-born descendants of Norwegian lepers. More often, they have come from the automatic merging of the findings of many workers in many lands. As with the milkmaid who assured Jenner that she was immune to smallpox because she had had cowpox, they have been given to the world by the folklore of simple people.

A quarter of a century after the epidemiology of yellow fever had been thought to be finally settled by Reed's successful transmission of the disease, foreshadowed by Finlay's hypothesis in Havana and made possible by Carter's establishment of the extrinsic incubation period in Orwood, Mississippi, the next important extension in knowledge of the epidemiology of yellow fever came with the establishment of a field laboratory by the Rockefeller Foundation in Lagos, Nigeria. Isolation of the virus and a blood test revealed that the disease was not limited to small areas on the west coast of Africa and east coast of Brazil, but that the virus actually was distributed from Dakar and Angola on the west coast, to Uganda and the Ethiopian foothills. In the Amazon valley, the belt of prevalence was extended to parts of Venezuela, Colombia, Ecuador, Peru, and Bolivia as well as Brazil, and a new species of mosquito was found to transmit the jungle type of yellow fever. Methods of

control of the fever carried by this sylvan *Hæmagogus capricornus* were entirely different from those for the city dwelling *Aëdes ægypti*, the mosquito which had been supposed to be the sole distributor of the disease.[8]

Thus, the epidemiologic knowledge of disease has been assembled from hypotheses originating in studies in all parts of the globe. Formerly, great epidemics followed large migrations of people and the development of new trade routes. Two striking examples are the dissemination of plague from Hong Kong by trading ships, and the breaking loose of Asiatic cholera from what was considered its native habitat to spread over Europe, Canada, and the United States in 1830. Some governments disregarded medical regulations entirely or even refused to admit the occurrence of epidemic disease within their own borders for fear of interrupting trade with others. Individual nations or cities attempted to check the entrance of disease by drastic measures at their ports and land borders. Some port authorities burned whole ships and their cargoes which had arrived from infected countries, or detained passengers and crew for long periods of quarantine.

With nations as with individual communities, the older idea of throwing the sick into pesthouses by law and under guard has given way to coöperation. We have learned that pestilential disease does not obey our laws but follows its own, traveling from one people to another, as we give it opportunity with our own travels. In the earlier decades of the 19th century, international coöperation in matters of health was instituted by the countries bordering on the Mediterranean Sea. The Turkish government, in 1839, invited representatives of other nations to meet with the Sanitary Commission of Constantinople for better regulations for ships with disease entering that port. This Commission extended its supervision to the ports of the Black Sea, the Straits, Asia Minor, and the Red Sea, and it provided sanitary regulations governing the pilgrimage to Mecca. The Egyptian Council assumed responsibility for the pilgrims of that region and after the opening of the Suez Canal (1869), it undertook medical supervision of traffic through that waterway.

In 1851, the first of a series of International Health Conventions was called in Paris. At this, and subsequent meetings in Constantinople, Vienna, Washington, Rome, Dresden, Venice and Paris, regulations were formulated concerning the notification of diseases such as cholera and plague, the medical inspection of departing crews and passengers from ports where certain diseases were known to exist; inspection and quarantine of those arriving from infected countries; and examination of certain types of cargoes likely to carry disease.

At the meetings of 1903 and 1907, the Office Internationale d'Hygiène Publique was established in Paris, and has continued to standardize methods of control of epidemic disease as between nations. It had the authority and financial support of 51 nations, and has been of great service in the field of international health. It has largely had to do with unifying the many national laws of sanitation. It has coördinated the health laws concerning pilgrimages from three continents to Mecca to prevent the exchange of cholera. It has aided in providing medical facilities in ports of all parts of the world for the treatment of sailors—in short, the international coöperation promoted by the Office d'Hygiène Publique can, perhaps, be best visualized in the large disks that can be seen on the hawsers of ships in port in all parts of the world, put there by mutual agreement to prevent the debarkation of rats which are the carriers of the bacillus of bubonic plague. Finally, the Health Section of the League of Nations was formed

to convene international conferences to exchange information and to take steps necessary to insure an effective international coöperation in matters of health. The Health Section of the League is the culmination of the efforts toward concerted action in preventing disease. It has made its influence felt in all parts of the world in combating epidemics, in standardizing medical biologic products, and in the prompt dissemination of information concerning the prevalence of epidemic disease everywhere.

Just as epidemiologic knowledge has been assembled from all parts of the world, it has been redistributed in its application to the prevention of disease by international coöperation at its best. International coöperation has not failed in this because the objective, freedom from disease, has been one on which all have agreed. No one anywhere gets sick by preference. The signal flag flown for quarantine inspection of ships is the same everywhere.

REFERENCES

(1.) Am. J. Pub. Health, 32, 414, 1942, and following issues. (2.) Aycock, W. L.: Am. J. Med. Sci., 201, 450, 1941. (3.) Bard, J.: An essay on the nature and cause of ye malignant pleurisy, 1749. (4.) Carter, H. R.: New Orleans Med. and Surg. J., 52, 617, 1900. (5.) Finlay, C.: Anales de la Real Academia de Ciencias Medicas; Fisicas y Naturales de la Habana, 48, 4, 1881. (6.) Hirsch, A.: Handbook of Geographical and Historical Pathology, translated from the German edition by Charles Creighton, London, The New Sydenham Society, vol. 1, 1883. (7.) Ibid., vol. 2. (8.) International Health Division of the Rockefeller Foundation—numerous publications. (9.) Reed, W., Carroll, J., Agramonte, A., and Lazear, J. W.: Phil. Med. J., 6, 790, 1900. (10.) Russell, F. F.: Virus and Rickettsial Diseases, Boston, Harvard Univ. Press, 1940.

BOOK REVIEWS AND NOTICES

A Handbook of Medical Library Practice. Editor, Janet Doe. Compiled by a Committee of the Medical Library Association. Based on a Preliminary Manuscript by M. Irene Jones. Pp. 609. Chicago: American Library Association, 1943. Price, $5.00.

Medical libraries have a number of special needs that will be met by this long-needed and long-contemplated handbook. Especially in the case of the smaller libraries, the librarian who starts better equipped with library training than with medical knowledge will benefit from the book as much as will his or her confrère who has been trained contrariwise. Of the 8 chapters, most are concerned with such matters as selecting and ordering, cataloging, handling of pictures and microfilms. There is a valuable final chapter on reference work, with an extensive Annotated List of Reference Books; the subject is so vast, however, that even its 174 pages cannot adequately cover the wide range. For instance, of 2 subjects taken at random, "Bibliographies of Aviation Medicine" includes but 2 items, neither of them being Fulton's. "Hæmatology (Encyclopedias, etc.)" includes 3 items: Downey, Kracke, Hirschfeld (in this order), Kracke however being but one of many 1-volume textbooks on the subject.

Especially interesting to the Reviewer is the chapter on Rare Books and the History of Medicine. More than half of the 115 pages is devoted to an Annotated Bibliography of books useful in a historical medical collection. As is fitting for a librarian's production, the book has a full and apparently accurate index.

Miss Doe and her 10 colleagues are to be congratulated on the production of a volume that is a valuable reference source to those interested in medical literature, and history, as well as an invaluable desk book for medical librarians.

<div style="text-align: right;">E. K.</div>

Medical Genetics. By Laurence H. Snyder, Sc.D., Professor of Medical Genetics, Ohio State University. Pp. 130; 24 figs. Durham, N. C.: Duke University Press, 1941. Price, $1.50.

The text material in this small volume is taken from a series of lectures presented to the medical schools of Duke University, Wake Forest College, and the University of North Carolina. Its contents include the study of human heredity, medico-legal applications, cancer, hereditary disorders of the different bodily systems, and a final chapter on the future development of medical genetics. It should aid in both the diagnosis and prevention of inherited diseases and abnormalities, and in giving correct advice to prospective marriages and pregnancies. All in all, it is a very satisfactory and useful compilation of data on this subject, and certainly a volume to be highly recommended to all clinicians and medical students. The emphasis rests on inherited abnormal states, whereas the principles of genetics are discussed only to the extent of giving us a concise understanding of the mechanisms involved.

<div style="text-align: right;">M. T.</div>

Atlas of Obstetric Technic. By Paul Titus, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh; Secretary, American Board of Obstetricians and Gynecologists. Illustrations by E. M. Schackelford, Medical Illustrator, John C. Oliver Memorial Research Foundation, St. Margaret Memorial Hospital. Pp. 180; 193 figs. St. Louis: C. V. Mosby Company, 1943. Price, $7.00.

It is said that a picture is worth a thousand words. On this assumption Titus's atlas with its 193 carefully selected illustrations should be a considerable

addition to textbooks dealing with obstetrics. In this volume the author has covered a wide range of subjects. In addition to illustrating strictly obstetrical topics, he considers in pictorial form such subjects as major and minor operations upon the abdomen which not infrequently complicate pregnancy, as well as technical procedures required in the treatment of patients suffering from sterility. A study of the pictures in this volume should give the medical student a clear comprehension of the subjects covered. The illustrations are line drawings of quite satisfactory size, and are described by carefully considered legends. One or more blank pages for notes or additional drawings are available at the end of each chapter.　　　　D. M.

PHYSIOLOGY IN AVIATION. By CHALMERS L. GEMMILL, B.S., M.D., Com., M. C., U. S. N. R., Associate Professor of Physiology, The Johns Hopkins University, School of Medicine, Baltimore, Md.; Instructor in Physiology, School of Medicine, Naval Air Station, Pensacola, Fla. With a chapter on Instrument Flight by LT. FREDERICK B. LEE, U. S. N. R. Pp. 132; 18 figs.; 18 tables. Springfield, Ill.: Charles C Thomas, 1943. Price, $2.00.

DR. GEMMILL, now on active service, has published in an entertaining and instructive book the lectures on the physiology of aviation given in the School of Aviation Medicine, Naval Air Station, Pensacola, Fla. In brief and succinct manner he has covered the essentials of physiology related to aviation problems. An interesting historical introduction is followed by chapters on the mechanics of respiration, on gas transport by the blood, on the circulation, on temperature control, and on the physiology of muscular exercise. The principles discussed are then applied to the problems arising in flight at high altitudes. Chapters are devoted to anoxia and aëroembolism, and also one on the effects of acceleration on man. A final instructive chapter on instrument flight by Lieut. Frederick B. Lee is appended.

Anyone interested in a clear, short account of the medical problems in this interesting field should read this book.　　　　W. S.

ESSENTIALS OF GYNECOLOGY. By WILLARD R. COOKE, M.D., F.A.C.S., Professor and Head of the Department of Obstetrics and Gynecology, University of Texas. Pp. 474; 197 illus., including 10 in color. Philadelphia: J. B. Lippincott Company, 1943. Price, $6.50.

THIS volume is a condensed textbook prepared for beginners in the subject. The various topics, though necessarily treated briefly, are satisfactory for the purpose. The illustrations include a number of excellent line drawings in addition to photographs of gross and microscopic specimens.

The material is well arranged and covers the clinical as well as the more academic aspect of the various subjects. The book is completely without reference to other works on the same subject. It should be of service to the medical student in securing the essentials of gynecology.　　　　D. M.

having chiefly a constitutional factor in their etiology, such as diabetes mellitus and diseases of the hemolytopoietic system.

Dr. Bauer finally lays down certain principles of treatment based on the defective constitutional etiology and points out certain pitfalls which one may encounter when these deficiencies are not adequately considered.

The real virtue of the book lies in its ability to stimulate thought as to the constitutional deficiencies which exist as part of the ordinary medical problems which confront every practitioner and as to how he may use these factors to modify his treatment to the patient's advantage. This book is highly recommended both to those actually engaged in the practice of medicine and to medical students.   J. S.

MODERN TRENDS IN OPHTHALMOLOGY. Edited by FREDERICK RIDLEY and ARNOLD SORSBY. Pp. 699; 217 figs; 8 color plates. First published in Great Britain, 1940. New York: Paul B. Hoeber, Inc., Medical Book Dept. of Harper & Bros., 1943. Price, $10.00.

THIS book brings various phases of Ophthalmology up to the last minute. The book is divided into 7 parts. The first part deals with the relation of ophthalmology to general medicine. In its first section on infection, allergy and immunity, of chief interest is the chapter on ophthalmologic conditions in tropical and subtropical regions. This will be of distinct value to ophthalmologists in the Armed Forces. Section 2 concerns the ocular manifestations of some general disturbances; it contains an excellent review on arteriosclerosis by Friedenwald. Section 3 deals with the ocular manifestations of some dystrophies.

The second part deals with diagnostic procedures; the third part with refraction and binocular vision; the fourth part, on the physiology of vision, contains a very good review by Selig Hecht. Part 5 groups together a number of unrelated subjects under the heading "new conceptions in pathology." Part 6 concerns modern treatment, and Part 7 the social aspects of ophthalmology. In this last chapter there is an article on chemical warfare in relation to ophthalmology.

As in compilations, some chapters are better than others, but it is an extremely valuable bibliography of the modern literature.   F. A.

MANUAL OF STANDARD PRACTICE OF PLASTIC AND MAXILLOFACIAL SURGERY. Military Surgical Manual I. Prepared and Edited by the Subcommittee on Plastic and Maxillofacial Surgery of the Committee on Surgery of the Division of Medical Sciences of the National Research Council, and Representatives of the Medical Department, U. S. Army. ROBERT H. IVY, Chairman. Pp. 432; 259 figs. Philadelphia: W. B. Saunders Company, 1942. Price, $5.00.

THIS is the first of a series of Military Surgical Manuals prepared under the auspices of the National Research Council for use by the Army and Navy as guides in the management of war casualties. The subject Plastic and Maxillofacial Surgery is very ably discussed. The text is divided into 4 parts: reconstructive surgery, maxillary surgery, maxillofacial prosthesis, and anesthetic technique. The subjects, although necessarily brief, are clearly and concisely presented. The book will be read and appreciated not only by those in the armed forces, but by many in civilian practice, for it is more than a simple war-time manual.   H. Z.

MEDICAL CLINICS OF NORTH AMERICA (St. Louis Number, Vol. 26, No. 2, March, 1942). Pp. 635; 26 ills. Philadelphia: W. B. Saunders Company, 1942. Price, $16.00 a year.

THIS volume maintains the usual high level of excellence of this bi-monthly publication. In this number, there are 14 fine articles on Medical Emergen-

cies, and a symposium of 6 articles on Tuberculosis. The 212 pages on Medical Emergencies form a handbook which every physician might well wish to have at hand in time of need. It is unfortunate that the 85 pages on Tuberculosis are inappropriately included in the same volume.

It is unfair to pick on minor points for criticism, but the lines on page 460 reading "Botulism—decomposed proteins and fats often found in cream or custards affect anterior horn cells of the spinal cord" seem so misleading and inaccurate as to deserve special mention.   O. P.

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Abdominal and Genito-urinary Injuries. Military Surgical Manual III. Prepared under the auspices of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Pp. 243; 28 figs. Philadelphia: W. B. Saunders Company, 1942. Price, $3.00.

This, the third manual of a series of Military Surgical Manuals prepared under the auspices of the National Research Council, is divided into two parts. The first deals with injuries of the abdomen; the second, with injuries of the genito-urinary tract. Diagnosis, surgical treatment, and subsequent care of the wounds are outlined. The text will serve to familiarize members of the medical forces of the Army and Navy with the type of wounds encountered in warfare.   H. Z.

Diseases of the Nose, Throat and Ear. By William L. Ballenger, M.D., F.A.C.S., Late Professor and Head of the Department of Otology, Rhinology and Laryngology, School of Medicine, University of Illinois; and Howard C. Ballenger, M.D., F.A.C.S., Associate Professor of Otolaryngology, Northwestern University School of Medicine, Chicago; Surgeon, Department of Otolaryngology, Evanston Hospital. Eighth ed. Pp. 975; 604 engravings, 27 plates (25 in color). Philadelphia: Lea & Febiger, 1943. Price, $12.00.

This has long been considered one of the leading text and reference books in Otolaryngology. The 1943 edition includes many new illustrations, the descriptions of some new operative procedures, the applications of the sulfonamides to Otolaryngology, as well as that wealth of information found in previous editions. It is not intended in any way to intimate by the brevity of this Review that the importance and excellence of the production is not thoroughly appreciated.   K. H.

Annual Review of Biochemistry. Vol. XII. Edited by James Murray Luck, Stanford University; Associate Editor, James H. C. Smith, Carnegie Institution of Washington, Division of Plant Biology, Stanford University, California. Pp. 704; many tables and figs. Stanford University P. O., California: Annual Reviews, Inc., 1943. Price, $5.00.

This volume, in addition to reviewing the subjects covered at frequent intervals (if not annually in this series), has several chapters devoted to subjects either appearing for the first time or which have not been reviewed for several years. Among these may be mentioned a chapter on Synthetic Drugs by T. C. Daniels, another on Carbon Dioxide Assimilation in Heterotrophic Organisms by H. A. Krebs and one on The Electron Microscope in Biology by L. Marton. Particularly in the last-mentioned chapter the author treats the subject not as an annual review but summarizes the work done since the building of the first compound instruments in 1932.

It appears that the war has not seriously decreased the quantity nor quality of the work which is being done in the field of biochemistry. This volume in every way meets the high standards set by the previous volumes.   J. J.

SKIN GRAFTING OF BURNS. By JAMES B. BROWN, M.D., LT. COL., M. C., U. S. A.; Senior Consultant in Plastic and Maxillofacial Injuries and Burns, E.T.O., U. S. A., Associate Professor of Surgery, Washington University, St. Louis; and FRANK McDOWELL, M.D., Assistant in Clinical Surgery, Washington University. Pp. 204; 131 illus. Philadelphia, London, and Montreal: J. B. Lippincott Company, 1943. Price, $5.00.

DURING a time of war the subject of burns becomes exceedingly important. The incidence rises enormously, not only on account of fire and explosions in battle situations but also because of the hazards to civilian workers in military industries. For this reason one welcomes the appearance of a monograph compiling the treatment experience of two of this country's most skilful plastic surgeons and epitomizing modern concepts of the skin grafting of burns. The book contains the following chapters: Early General Care, Early Local Care, Preparation of Wounds for Skin Grafting, Application of Thick Split Grafts, Application of Free Full Thickness Grafts, Pedicle Flaps, Regional Repairs of Trunk and Extremities, Regional Repairs of Head and Neck, Homografts, Faults of Skin Grafts, Treatment of Burns in World War II. The excellent paper, large type and clear illustrations make for easy understanding of the recommended techniques. Many of the illustrations and case reports will be recognized by those who have been following the authors' writings in the surgical journals. Dr. Brown's note from the European theatre of operations in the Preface brings the timeliness of the book up to May 6, 1943, when this addendum was written.

The deficiencies of the book are minor and do not in any sense detract from the value of the material contained within it. No mention is made, for instance, of Roentgen ray burns. A description of the differences in lesions resulting from different burning agents such as heat, steam, electricity, Roentgen rays and friction would be helpful. There is but a brief discussion of the use of the dermatome, which in many hands has proved efficient, and the subject of full thickness grafts does not receive much emphasis. The chapter on faults and failures of skin grafts is far too short. No reference is made to constitutional reactions following the dusting of sulfonamides on granulating areas.

Merely as a treatise on the thick split graft, at which procedure the authors are unsurpassed, this book is worth far more than its purchase price.

I. W.

YOUR ARTHRITIS: What You Can Do About It. By ALFRED E. PHELPS, M.D. Introduction by R. GARFIELD SNYDER, M.D. Illustrations by JAMES MacDONALD. Pp. 192; 12 illus. New York: William Morrow & Co., 1943. Price, $2.00.

THIS book, a summary of present knowledge of arthritis, written for the laity, fills a definite need. It should also be known to all who treat these patients, for its recommendation will save the busy practitioner precious hours by anticipating many questions. Causes, course of disease and treatment are conservatively and thoroughly discussed.

W. S.

SYNOPSIS OF BLOOD DISEASES. By A. PINEY, M.D., M.R.C.P., Director, Pathological Department, Royal Cancer Hospital, London; Physician, St. Mary's Hospital for Women and Children, London. Pp. 120; 4 plates and several tables. Philadelphia: The Blakiston Company, 1942. Price, $2.75.

THIS is a rigidly skeletonized compendium of hematology, presented in telegraphic style. Most of the subject matter of hematology is adequately covered, if due allowance is made for the limitations of a work of this nature. Particular value attaches to the diagnostic outlines. Certain faults are apparent. The rapid style is sometimes careless and incoherent. The brief

statements are sometimes overly dogmatic. Hemoglobin is measured in percentage, but no standard value is given. It is wrongly stated that the anemia of sickle cell anemia can usually be relieved with iron and liver extract. British pharmaceutical proprietaries, unfamiliar in this country, are unfortunately frequently recommended in delineations of therapy. No mention is made of "unit" assay and dosage of liver extract in the treatment of pernicious anemia. The importance of sulfonamides, and of Rh factor, goes untouched in the discussion of hemolytic syndromes. The illustrations of the various blood and marrow cells (in color) are schematic. On the whole, however, the work is a useful "refresher," if judiciously read.   A. C.

METHODS OF TREATMENT. By LOGAN CLENDENING, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals; and EDWARD H. HASHINGER, A.B., M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals; Attending Physician, St. Luke's Hospital, Kansas City, Mo. With chapters on Special Subjects by various authors. Eighth ed. Pp. 1033; 138 figs. St. Louis: C. V. Mosby Company, 1943. Price, $10.00.

"THIS book is planned to furnish an outline of all the methods of treatment in internal medicine." What the authors have done, in effect, is to set under one cover the sections usually devoted to treatment in the standard texts on Medicine, Surgery, and some of the specialties.

Part I describes the procedures under headings such as Rest, Drugs (an epitomized pharmacology text), Anesthesia, Immunology, Allergy, Dietetics, Infant Feeding, Physical Therapy, Radiotherapy, Spas, Psychotherapy, and Miscellaneous Procedures such as Blood Transfusion, Spinal Puncture, etc. Part II discusses the application of these procedures for the specific conditions.

It is difficult to know what group might find the book useful—it is too elementary for the specialist, too epitomized and "compended" for the student. The general practitioner may find it helpful as a handy reference in the management of some conditions, or in a procedure perhaps better executed by someone trained in this field. In no sense are the directions complete. Example: For abdominal paracentesis: "The patient should empty his bladder." No mention is made of catheterization. The experienced will not need the few simple directions that are included, while the neophyte will not think of the important step of being sure the bladder is empty by catheterization. No mention is made of recording blood pressure for impending circulatory collapse during the procedure, the use of the abdominal binder, or the procedure to be carried out should the trocar enter bladder or bowel. The use of the oscillating bed is advised, without critical comment, in the treatment of congestive heart failure. Venesection is dismissed, after a short historical account, with the statement "It may be done in pneumonia, uremia, hypertension, and in the premonitory signs of cerebral apoplexy." Indications, among contraindications, results, etc., are omitted. The technique of instilling iodized oil into the trachea is described for use in the Roentgen diagnosis of bronchiectasis. The action of radium on cancer is discussed in generalities, as is the entire chapter on Radiotherapy, admittedly for student and general practitioner, not for the radiologist. The author's style recalls the senior and entertaining "Human Body," a popular style full of anecdotes, but not of great value for the physician and lacking notably in essential detail.

There is little in the book that could not be read to better advantage in current standard work. However, in the words of the authors: "All therapeutic procedure is brought together within the compass of one book. Nowhere else, so far as we know, is such a plan carried out. It is the justification we have for the book's existence." The text is therefore recommended, but with reservations.   E. V.

WHOOPING COUGH. By JOSEPH H. LAPIN, B.CHEM., M.D., Adjunct Pediatrician, Bronx Hospital; Associate in Contagion, Riverside Hospital for Contagious Diseases, New York. Pp. 237; 25 tables, 40 illus. Springfield, Ill.: Charles C Thomas, 1943. Price, $4.50.

MUCH interest is being shown currently in whooping cough, despite, or perhaps in part because of, the refractoriness of this affection to the sulfonamide drugs. Here is a new monograph of medium size, readable and well balanced, condensing what is known and emphasizing what remains unknown. The author is a pediatrician with a wide personal experience with the disease, both in the clinic and the laboratory. He presents stock-taking chapters on history, epidemiology, bacteriology, pathology, immunology, serology, clinical manifestations, hematology, roentgenology, complications, diagnosis, prophylaxis of non-exposed children, prophylaxis of "contacts," specific treatment, nonspecific treatment, treatment of complications, and public health considertions. Every chapter is divided into well-organized subsections, and all material is presented from the practical clinical point of view.

With regard to the controversial value of vaccine prophylaxis for building active immunity, the author summarizes the results of 26 studies by different workers. According to the best evidence, immunization will reduce the attack rate to from 10% to 35% of that for unvaccinated controls. The communicability rate for intimate sibling exposures is about a third of the figure for unvaccinated controls. There is general agreement that attacks which occur in vaccinated children are markedly lighter than in unvaccinated children. The duration of immunity is still in doubt, but is probably several years, at least. Vaccines are apparently best prepared from *H. pertussis* in Phase I. These are freshly isolated strains with smooth colonies, virulent for animals, and containing in their surfaces an antibody-stimulating antigen which becomes completely lost upon repeated subculture. Of the specific forms of treatment, human sera, convalescent or hyperimmune, have received more encouraging reports than have animal sera or vaccines prepared from the whole Bordet-Gengou bacillus or its fractions.

Bacteriologic examination with the well-known cough plate method is still the most valuable single laboratory aid in the catarrhal stage of the infection. The difficulty, however, in getting a vigorous cough in infants at the proper times has led to poor success in diagnosis with this age group. Bradford and others have introduced recently the taking of nasopharyngeal swabs in suspected cases during infancy, and their results have been highly favorable.

Well-chosen illustrative data, excellent photographs and carefully selected bibliographic references contribute to the value of this review. I. W.

NOXIOUS GASES and the Principles of Respiration Influencing Their Action. By YANDELL HENDERSON and HOWARD W. HAGGARD, from the Laboratory of Applied Physiology, Yale University. American Chemical Society Monograph Series. Second ed. Pp. 294, various tables. New York: Reinhold Publishing Corp., 1943. Price, $3.50.

THIS revised edition is an excellent treatise covering the many aspects required in a thorough consideration of the noxious gases. These gases are classified according to their chemical composition and by their physiologic actions. Their list is extremely comprehensive and includes anesthetics and volatile drugs, as well as many other substances seldom embraced in the category of noxious gas.

Among the subjects treated are the laws of gases and vapors, complete with tables and formulæ for the calculations of specific problems involving them. Finally, the clinical manifestations resulting from the inhalation of each gas and the therapeutic methods for combating them are discussed.

This work is remarkably inclusive and its material is excellently presented. It is a valuable reference volume for physicians in general and should prove indispensable to those harried by industrial problems. C. C.

METHODS FOR DIAGNOSTIC BACTERIOLOGY. By ISABELLE G. SCHAUB, A.B., Instructor in Bacteriology, Department of Pathology and Bacteriology, The Johns Hopkins University School of Medicine; Bacteriologist in Charge of the Diagnostic Bacteriological Laboratory of the Woman's Clinic, The Johns Hopkins Hospital; Instructor in Bacteriology in the Nurses Training School; and M. KATHLEEN FOLEY, A.B., Bacteriologist in Charge of the Diagnostic Bacteriological Laboratory of the Medical Clinic, The Johns Hopkins Hospital. Second ed. Pp. 430. St. Louis: C. V. Mosby Company, 1943. Price, $3.50.

THIS is a new edition of the manual of bacteriologic procedures and techniques as practised at the authors' hospital. In the 200 pages of text, the procedures for the isolation and identification of human pathogens are well outlined. The book contains 3 parts: I. Bacteriological Diagnosis, II. Serological Diagnosis, and III. Media, Stains, Reagents and Tests. A new chapter (Chapt. 2) has been added—the rapid identification of pathogens by colony morphology.

The authors stick mainly to one procedure for each test—a tried and true one. Many laboratories might find this manual inadequate for their needs. Especially true would this be in the Wassermann reaction, other complement fixation tests and flocculation tests being entirely neglected.

While not covering the entire field of diagnostic bacteriology and immunology, it does bring together many proven techniques and procedures of great value to medical students, internes and technicians in diagnostic laboratories.

F. E.

ESSENTIALS OF SYPHILOLOGY. By RUDOLPH H. KAMPMEIER, A.B., M.D., Associate Professor of Medicine, Vanderbilt University School of Medicine; in Charge of the Syphilis Clinic and Visiting Physician to Vanderbilt University Hospital. With chapters by ALVIN E. KELLER, M.D., and J. CYRIL PETERSON, M.D. Pp. 518; 87 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $5.00.

THIS well-written book is another in the series of "Essentials" being published by the Lippincott Company. It represents an attempt by the author to meet the needs of the practitioner of medicine in the field of syphilology.

Although the author makes no claim to originality, the material is interspersed with the results of his investigations and those of his colleagues, as well as case material from his Vanderbilt University Syphilis Clinic. On the whole, whoever, the viewpoints expressed are more or less standard.

The volume does not seem to the Reviewer to fulfill entirely the need for a text "written by a general practitioner for the general practitioner," as it does not supply, for instance, sufficient working technical details, for the relatively uninformed, of such procedures as drug mixing, technique of drug administration, lumbar puncture, and so forth.

Late syphilis, the practitioner's chief problem, is only briefly described. Little attempt is made to suggest the need for competent consultation, so that the practitioner may feel that these brief descriptions of visceral syphilis are adequate to guide him in practice.

In spite of such items, however, we regard the work as a good "refresher" text for rapid, up-to-date review of the "Essentials" of syphilology in all its phases, medical and social.

H. B.

VITAMINS AND HORMONES. Edited by ROBERT S. HARRIS, Associate Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, and KENNETH V. THIMANN, Associate Professor of Plant Physiology, Harvard University. Vol. I. Foreword by E. V. McCOLLUM, Johns Hopkins University. Pp. 452; many tables and figs. New York: Academic Press, Inc., 1943. Price, $6.50.

According to the Editors this is the first of what is hoped to be a series of yearly volumes on Vitamins and Hormones which will chronicle progress

and point the way to new achievements." The subjects covered in the first volume, with the authors of each, are as follows: (1) Choline—Chemistry and Significance as a Dietary Factor, by C. H. Best and C. C. Lucas; (2) The Appraisal of Nutritional States, by Norman Jolliffe and Rita M. Most; (3) Physical Methods for the Identification and Assay of Vitamins and Hormones, by John R. Loofbourow; (4) The Chemical and Physiological Relationship Between Vitamins and Amino Acids, by H. H. Mitchell; (5) The Photoreceptor Function of the Carotenoids and Vitamin A, by George Wald; (6) The Significance of the Vitamin Content of Tissues, by Roger J. Williams; (7) GrowthFactors for Protozoa, by Richard P. Hall; (8) Physiology of Anti-Pernicious Anemia Material, by George R. Minot and Maurice B. Strauss; (9) The Intermediate Metabolism of the Sex Hormones, by Gregory Pincus and William H. Pearlman; (10) The Hormones of the Adrenal Cortex, by T. Reichstein and C. W. Shoppee.

To any one familiar with the field of Nutrition or Physiology it need not be stated that all of the authors are recognized leaders in their field. This fact is very obvious as one reads the various articles, for they are both a condensation of the literature and critical reviews of the work which has been done. Investigators in the field of nutrition will find that this volume not only helps in becoming familiar with the literature on the various subjects discussed but that it also will be an aid in separating the wheat from the chaff. It is hoped that future volumes will be written in a similar vein. There are surprisingly few typographic errors.

J. J.

ALLERGY. By Erich Urbach, M.D., Chief of Allergy Service, Jewish Hospital, Philadelphia; Associate in Dermatology, University of Pennsylvania School of Medicine; and Philip M. Gottlieb, M.D., Associate on Allergy Service, Jewish Hospital, Philadelphia; Instructor in Medicine, University of Pennsylvania School of Medicine. Pp. 1100; 40 illus; 80 tables and charts. New York: Grune & Stratton, Inc., 1943. Price, $12.00.

A vast increase in our knowledge of human hypersensitivity has accumulated in the past 15 years. Much of this is controversial or conjectural; thus, a text in its relatively new field is of timely interest.

The major part of the book has been written essentially for the clinician, particularly the internist. The subject matter is well arranged and well presented. Part I presents the basic science of allergy—written as an orientation and as reference material. Part II deals with the common etiologic agents, but omits the technical details such as botanical history of the pollen producers, etc. In Part III the author discusses the various diseases from the clinical and therapeutic points of view. In this section a chapter is given to the manifestations of allergy in each system, that is, Upper Respiratory Tract, Lower Respiratory Tract, Gastro Intestinal System, Liver and Gall Bladder, Skin, Nervous System, Eye, etc. The two final chapters deal with allergy in the very young, and in the aged—a welcome inclusion for those wishing to add to their repertory of geriatric principles. Graphic calendars of seasonal polination periods, diet charts, regimen outlines, testing media, and indicated medication provide an array of practical tools for the allergist. Of particular value is the replete system of cross-references which the neophyte allergist should find helpful in finding his way among the new terms introduced. The index is complete, and, with the reference system, the text can be used as an aid in finding the cause and treatment of an allergic disorder. The section devoted to asthma (110 pages) approaches monographic proportions. The reference sources, although chiefly English and American, include many in foreign languages. While numerous, the references are select; they are listed at the bottom of each page. Dr. Urbach expresses his own opinion freely, particularly on controversial material, and includes a minimum of information that must, to date, be classed as speculative. The author tends to dispel certain prevalent misconceptions, notably the inadequacy of skin

testing (which explains the disrepute into which this practice is falling). The truly remarkable specificity of the antigen-antibody reaction, the limitations of climatotherapy and the distinction between local hypersensitivity and the ability of the contactant to act as a primary irritant are topics worthy of note. The text should prove of great practical value to those with general or special interest in this field, and is heartily recommended.   E. W.

MEMOIR OF WALTER REED. The Yellow Fever Episode. By ALBERT E. TRUBY, Brigadier General, U. S. A., Retired. Pp. 239; 29 figs. New York and London: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1943. Price, $3.50.

IN his earnestness to present all the documentary and factual data pertaining to the discovery of the cure and prevention of yellow fever, the author, for some at least, has sacrificed reader-interest. Without a doubt the yellow fever episode is one of intense dramatic interest—happening as it has within the lifetime of many of us. An untold amount of material has been written about different phases of the study; and naturally distortion of facts has crept into some of these writings. Thus, the purpose of the author has been to "clear up all doubtful or disputed points, to evaluate, as far as possible, the part played by each of the chief actors and to make an authentic and factual history of the great demonstration." Inasmuch as Brigadier General Truby was one of the main actors in this drama, he is well qualified to follow out his objective.

There is no doubt in the mind of the Reviewer that the author has set forth the pertinent facts with great accuracy and painstaking detail. It is merely unfortunate that such painstaking detail should detract from the vividness of the characters portrayed, so that they tend to become names on a page and fail to stand forth as human beings. Even though the great personality of the book, Walter Reed, is talked about from almost the first page—one still does not have a clear conception of Reed the Man. His reputation as a scientist was established before his untimely and early death from appendicitis, so that this book is not concerned with building him up from that angle—but we still do not actually know the human side of the great scientist, and this would have added much to the interest of the book. Yet we must not lose sight of the fact that such a book as this should be written, so that as history attains more of a perspective on this medical epoch, true facts will not become distorted or lost as the active participants disappear from the scene.   E. F.

NEW BOOKS

Allergy. By ERICH URBACH, M.D., Chief of Allergy Service, Jewish Hospital, Philadelphia; Associate in Dermatology, University of Pennsylvania School of Medicine; and PHILIP M. GOTTLIEB, M.D., Associate on Allergy Service, Jewish Hospital, Philadelphia; Instructor in Medicine, University of Pennsylvania School of Medicine. Pp. 1100; 400 illus., 80 tables and charts. New York: Grune & Stratton, Inc., 1943. Price, $12.00. (Reviewed, p. 417.)

Annual Review of Biochemistry. Vol. XII. Edited by JAMES MURRAY LUCK, Stanford University; Associate Editor JAMES H. C. SMITH, Carnegie Institution of Washington, Division of Plant Biology, Stanford University, California. Pp. 704; many tables and figs. Stanford University P. O., Calif.: Annual Reviews, Inc., 1943. Price, $5.00.

Dictionary of Biochemistry and Related Subjects. Editor-in-Chief, WILLIAM M. MALISOFF, Professor of Biochemistry at the Polytechnic Institute of Brooklyn. Pp. 579. New York: Philosophical Library, Inc., 1943. Price, $7.50.

Hundreds of Problems. By STANLEY COBB, Bullard Professor of Neuropathology, Harvard Medical School, Psychiatrist-in-Chief, Massachusetts General Hospital. Harvard University Monographs in Medicine and Public Health, #4. Pp. 169; 2 figs. Cambridge, Mass.: Harvard University Press, 1943. Price, $2.50.

A Synopsis of Clinical Syphilis. By JAMES KIRBY HOWLES, B.S., M.D., M.M.S., Professor of Dermatology and Syphilology, and Director of the Department, Louisiana State University School of Medicine; Senior Visiting Physician, Charity Hospital of Louisiana at New Orleans; Visiting Physician, French Hospital, Mercy Hospital, Hotel Dieu, Southern Baptist Hospital and Touro Infirmary. Pp. 761; 121 illus., 2 color plates. St. Louis: C. V. Mosby Company, 1943. Price, $6.00.

Memoir of Walter Reed. The Yellow Fever Episode. By ALBERT E. TRUBY, Brigadier General, United States Army, Retired. Pp. 239; 29 figs. New York, London: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1943. Price, $3.50. (See Review, p. 418, this issue.)

Rehabilitation of the War Injured. Edited by WILLIAM BROWN DOHERTY, M.D., and DAGOBERT D. RUNES, PH.D. Pp. 684; many figs. New York: Philosophical Library, 1943. Price, $10.00.

The Boy Sex Offender and His Later Career. By LEWIS J. DOSHAY, M.D., PH.D., Psychiatrist, Children's Courts, New York City; formerly Senior Assistant Physician, Manhattan State Hospital, and Attending Specialist in Neuropsychiatry, U. S. Veterans Hospital, New York City. Pp. 248; 40 tables, 12 diagrams. New York: Grune & Stratton, 1943. Price, $3.50.

The Microscope and Its Use. By FRANK J. MUNOZ, Technical Microscope Consultant; in Collaboration with DR. HARRY A. CHARIPPER, Professor of Biology, New York University. Pp. 334; 122 figs. Brooklyn, N. Y.: Chemical Publishing Company, Inc., 1943. Price, $2.50.

Cytology and Cell Physiology. Edited by GEOFFREY BOURNE. Pp. 296; several figs. and plates. New York: Oxford University Press, 1942. Price, $6.00.

Medical Clinics of North America. Symposium on Physical Therapy. Mayo Clinic Number. Pp. 317. Philadelphia: W. B. Saunders Company, 1943. Price, $16.00 per year.

Addendum to the Chemistry of the Amino Acids and Proteins. Edited by CARL L. A. SCHMIDT, M.S., PH.D., Professor of Biochemistry and Dean of the College of Pharmacy, University of California. This is a supplement to the Second edition. Pp. 155; figures and tables. Springfield, Ill.: and Baltimore, Md.: Charles C Thomas, 1943. Price, $5.00.

NEW EDITIONS

Methods of Treatment. By LOGAN CLENDENING, M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals; and EDWARD H. HASHINGER, A.B., M.D., Clinical Professor of Medicine, Medical Department of the University of Kansas; Attending Physician, University of Kansas Hospitals; Attending Physician, St. Luke's Hospital, Kansas City, Mo. With chapters on Special Subjects. Eighth ed. Pp. 1033; 138 figs. St. Louis: C. V. Mosby Company, 1943. Price, $10.00. (See Review, p. 414, this issue.)

Clinical Parasitology. By CHARLES F. CRAIG, M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Col., U. S. Army (Retired), D.S.M., Emeritus Professor of Tropical Medicine in The Tulane University of Louisiana, New Orleans; and ERNEST C. FAUST, M.A., PH.D., Professor of Parasitology in the Department of Tropical Medicine, The Tulane University of Louisiana. Third ed. Pp. 767; 284 illus., 4 colored plates. Philadelphia: Lea & Febiger, 1943. Price, $9.00.

Roentgenographic Technique. By DARMON A. RHINEHART, A.M., M.D., F.A.C.R., Professor of Roentgenology and Applied Anatomy, School of Medicine, University of Arkansas; Roentgenologist to St. Vincent's Infirmary, Missouri Pacific Hospital, and the Arkansas Children's Hospital, Little Rock. Third ed. Pp. 471; 201 engrav. Philadelphia: Lea & Febiger, 1943. Price, $5.50.

A Workbook of Elementary Pharmacology and Therapeutics. By LUELLA C. SMITH, M.D., B.S. Second ed. Pp. 300. St. Louis: C. V. Mosby Company, 1943. Price, $2.00.

THIS loose-leaf book is primarily an extensive review of mathematics for nurses with emphasis upon the preparation of solutions and hypodermic doses and upon conversion from metric to apothecaries system. Some practical information concerning the administration of drugs is included in the last third of the book, but this can scarcely be called pharmacology in the modern sense. It is worth noting that the major portion of the book would be unnecessary if the medical and nursing professions would adopt the metric system.   J. C.

The Modern Treatment of Syphilis. By JOSEPH EARLE MOORE, M.D., Associate Professor of Medicine and Adjunct Professor of Public Health Administration, The Johns Hopkins University; Physician-in-Charge, Syphilis Division of the Medical Clinic, and Visiting Physician, The Johns Hopkins Hospital, Baltimore; Special Consultant, United States Public Health Service. With the Collaboration of JAROLD E. KEMP, M.D., HARRY EAGLE, M.D., APUL PADGET, M.D., MARY S. GOODWIN, M.D., FRANK REYNOLDS, M.D., of whom all are members of the faculty of the Johns Hopkins University. Second ed. Pp. 717; 109 figs. Springfield, Ill., and Baltimore, Md.: Charles C Thomas, 1943. Price, $7.00.

THIS fresh version is a reprint of the first 32 chapters of the 2d edition without changes, while Chapter 33 on "Intensive Arsenotherapy of Early Syphilis" is completely rewritten and brought up-to-date and there is an addition of a 34th chapter on "Venereal Disease Control in the Army and Navy." Since a critical review of the first 32 chapters has recently appeared in this Journal (204, 120, 1942) it remains only to mention that Moore and his associates have provided a fruitful source of reference material for two pressing problems in today's Syphilology.   H. R.

CORRECTION

In the Progress article by Mary Benson Hall on "Nausea and Vomiting of Pregnancy" appearing in the June number of this Journal, p. 872, Reference 56 (Strauss, M. B.) should be changed to 36 (Luikart, R.).

NEW NOTICE TO CONTRIBUTORS AND SUBSCRIBERS

ORIGINAL ARTICLES

INTRADERMAL TEST FOR SUSCEPTIBILITY TO AND IMMUNIZATION AGAINST WHOOPING COUGH USING AGGLUTINOGEN FROM PHASE I H. PERTUSSIS[*]

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At the present time, 4 substances are available for use as reagents in skin testing for susceptibility to whooping cough. These are suspensions of killed *Hemophilus pertussis*, extracts of these bacterial cells, purified toxin and purified agglutinogen. The first 2 reagents have proven unsatisfactory because they represent gross mixtures of the several components of the bacteria and these individual components have conflicting reactive properties. Attempts to classify tested individuals into immune and susceptible groups with these 2 reagents have given confusing and overlapping results. Strean's results[9] with purified toxin indicate that this reagent does not distinguish between susceptible individuals and those who have been successfully immunized with killed whole Phase I *H. pertussis* cells, such as composed the vaccines of Sauer,[7] Kendrick and Eldering,[4] Miller and Faber,[5] Singer-Brooks,[8] and others. This purified toxin apparently distinguishes from the susceptibles only those recovered from the disease and those immunized with toxoid.

The rationale of the use of agglutinogen in such a test has been discussed previously.[2,3] Results obtained until now with the

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test have shown that purified agglutinogen accurately classifies the immune and the susceptible individuals in accord with their histories, both of incidence of disease and of vaccination. A detailed analysis of some of the first clinical results obtained is reported elsewhere.[1] The test itself and the method of carrying it out are described here for the first time and the significance of the results is discussed. The total number tested and which are now being reported has been extended to 931.

Method. Ten units of agglutinogen in a volume of 0.1 ml. of 0.85% sodium chloride solution are used for intradermal injection. The container with dry agglutinogen is scratched with a file and opened in the usual fashion. The proper quantity of sodium chloride solution is added. The agglutinogen will be found to dissolve instantly, and after slight agitation it is withdrawn into a syringe. A preservative is not added because one not causing deterioration of the product or a false positive reaction in certain individuals has not been found. Unused agglutinogen should not be stored after dissolving, unless kept frozen, because of possible contamination.

The intradermal injection is made in the usual fashion. In immune children, two types of response may be obtained: the immediate or wheal-like reaction, and the delayed or tuberculin type of reaction. Some children may show both, some one or the other. Readings are made at two times, ½ hour and about 24 hours after injection. Induration is the determinant factor in a positive immune reaction to distinguish it from a negative susceptible reaction. Rubbing the finger over the site of injection frequently may aid in determining the extent of the reaction. Erythema may or may not be present and if present alone should not be considered. Erythema without at least some induration normally is not observed, and in the event that a non-indurated reaction should be suspected, it should be examined very carefully. If it definitely is nothing more than a flare of redness, the reaction should be classified as negative susceptible.

An area of 10 mm. is regarded as the upper limit for a negative reaction, this allowance being necessary because certain normal skins give a slight response to the trauma of the injection. No untoward local or systemic reactions have been observed in the approximately 1000 children tested so far.

The following has been used as a classification for grading the reactions:

PI—positive immune: a well-indurated reaction (with or without erythema) 20 mm. or more in diameter at either ½ hour or 24 hours or both.

WPI—weakly positive immune: an indurated reaction (with or without erythema) not exceeding 20 mm. in diameter at either ½ hour or 24 hours, but at least 10 mm. in diameter at either time or both.

NS—negative susceptible: no indurated reaction at either ½ hour or 24 hours beyond an area 10 mm. in diameter.

The reaction will be found to fade quickly, and usually in 36 hours or more will have disappeared. In negro children, immune or susceptible, some residual pigmentation may be observed, which is not abnormal in this race after intradermal injection.

Results. The results obtained in 650 children with known histories are summarized in Table 1. The histories were obtained from various institutions and clinics. Perhaps of greatest significance is the fact that only one child with a negative history showed a false positive reaction. The pattern or distribution of results obtained in those with positive histories of either the disease or of having been vaccinated is reasonable; a solid or even partial immunity in all individuals of these two positive groups is not to be expected. Among other factors

the children in the study having a positive history of the disease, did not have the diagnosis confirmed bacteriologically. There is always the possibility of B. parapertussis having been the causative agent and a positive immune reaction in such a case would not be expected. Some of those in the vaccinated group were from an institution where it was found subsequently that the vaccine used was of low potency.

TABLE 1.—RESULTS OF SKIN TESTING WITH AGGLUTINOGEN

Reaction	No history of disease or vaccination		History of whooping cough		Vaccinated	
	No.	%	No.	%	No.	%
Positive	1	<1	116	53	174	56
Weakly positive	0	0	78	36	114	36
Negative	121	>99	24	11	23	8
Total	122	100	218	100	311	100

The inclusion of an intermediate group, WPI (weakly positive immune) we believe should be of considerable interest. All immunity is relative. There are those with an intermediate or partial degree of immunity in whom the protection may be sufficient only when the exposure is not overwhelming and when the general resistance has not been lowered. The WPI group may serve to detect those individuals who have such a partial immunity.

In a child without known history of the disease or of vaccination, there may be some immunity as a result of contact or subclinical infection. It should not be surprising occasionally to find some degree of immunity indicated by the test in such a case. For this reason, in the present study, in the control group were included only babies within the age group of 6 to 14 months. In this group it is improbable that immunity might exist because whooping cough seldom occurs with sufficient mildness at this age to go undiagnosed. Under 6 months of age, of course, the skin cannot be assumed to act reliably.

A group of 281 "unknown" older children were tested. Of these, 45% showed a positive immune reaction, and 31% a weakly positive immune reaction.

Agglutination titers were determined in 173 children before skin testing. It was found that all those having an agglutination titer of 1 to 20 or higher give a positive, or weakly positive, skin test indicating at least some degree of immunity. On the other hand, individuals having no agglutination titer may also give a positive or weakly positive skin test indicating some degree of immunity. The explanation seems to be that the test is an indicator of fixed antibodies. On this basis the test is positive, at least to a limited extent, in all of those having circulating antibodies and also in those having only fixed antibodies and without detectable circulating antibodies. This suggests an explanation of the failure of agglutination titers to provide an accurate prediction of susceptibility to whooping cough, fixed antibodies not being detectable by agglutination. In harmony with these considerations Miller and collaborators, in a recent study with 554 children, have shown that whereas a negative agglutinative titer does not neces-

sarily indicate susceptibility, a significant positive titer does indicate clinical immunity.

It is striking that a single skin test injection of agglutinogen produces a marked rise in the agglutination titer of serum from those individuals showing a positive or weakly positive reaction initially. This increase in agglutination titer occurs regularly in all cases even though the titer initially may have been zero. (Of course, there is no increase in agglutination titer as a result of the test where initially the titer is high and close to the usual ceiling.) In some cases, the agglutination titer as a result of a single injection may rise from zero to as high as 1 to 10,000.

In 65 of the children, it was possible to obtain blood 10 months after the test had been performed. The agglutination titers were determined and it was found that in all cases the elevation in titer had persisted. In just a few cases, there was a slight decrease from the peak reached. None showed a major decrease in titer.

Those individuals giving a negative skin reaction require repeated skin test doses in order to reverse the test and to produce a significant agglutination titer. Usually 3 such doses are required.

These results suggest that agglutinogen might prove to be a valuable reagent for use in immunization, as well as for determination of susceptibility. Particularly would the reagent be of value for skin testing at some time following the primary vaccination. Used at this time in a single dose, the reagent would serve both to determine the degree of immunization resulting from the primary vaccination and as a "stimulation" reagent for immunization. This would fit in well with the currently favored procedure of stimulation of immunity to whooping cough at about a year following the primary vaccination in order to produce a more nearly complete immunity.

In a careful study of a small institutional epidemic, it was indicated that the use of agglutinogen as a skin test reagent accurately predicted susceptibility. Also apparently the partial immunity of many individuals was stepped up enough to protect them from the current infection. Thus the number of susceptible individuals was definitely decreased. From the epidemiologic point of view, this is a very fortunate finding because by means of this test not only are those few highly susceptible individuals singled out, but those with a partial immunity become more adequately protected.

Conclusion. It appears from this study that the purified agglutinogen of *H. pertussis* should provide, as expected,[?] an excellent reagent for assisting in control of whooping cough. This would be not only in detecting which individuals in a group are susceptible, but also in stimulating immunity in those having but a partial degree at the time of the test.

Summary. The skin test utilizing purified pertussis agglutinogen as a reagent classifies immune and susceptible individuals in accord with their history of incidence of infection and vaccination with *H. pertussis*. The test can also be used as a means of stimulation of immunity at a time following primary vaccination, as well as to determine the degree

of immunity resulting from the primary vaccination itself. In those individuals having an existing immunity to pertussis at the time of the test, a marked increase is produced in the agglutination titer. In those with no initial immunity, repeated doses will produce a reversal of the test and an agglutination titer. The reagent gives promise of value, at the time of epidemics, not only to determine those who are susceptible, but also to increase the degree of immunity in those having but a partial immunity to pertussis.

ADDENDUM.—The preparation of agglutinogen following acid extraction has been described by Smolens and Mudd[8a]; this may be simpler as well as providing a method which can be more generally applied.

REFERENCES

1. FELTON, H. M., and FLOSDORF, E. W.: J. Pediat., 22, 259, 1943.
2. FLOSDORF, E. W., and KIMBALL, A. C.: J. Immunol., 39, 475, 1940.
3. FLOSDORF, E. W., and McGUINNESS, A. C.: Am. J. Dis. Child., 64, 43, 1942.
4. KENDRICK, P., and ELDERING, G.: Am. J. Hyg., 29, 133, 1939.
5. MILLER, J. J., and FABER, H. K.: J. Am. Med. Assn., 112, 1145, 1939.
6. MILLER, J. J., JR., SILVERBERG, R. J., SAITO, T. M,, and HUMBER, J. B.: J. Pediat., 22, 644, 1943.
7. SAUER, L. W.: J. Am. Med. Assn., 112, 305, 1939.
8. SINGER-BROOKS, C. H.: J. Pediat., 14, 25, 1939; J. Am. Med. Assn., 114, 1734, 1940.
8a. SMOLENS, J., and MUDD, S.: J. Immunol., 47, 155, 1943.
9. STREAN, L. P., LAPOINT, D., and DECHENE, E.: Canad. Med. Assn. J., 45, 326, 1941.

THYROTOXICOSIS AS THE SOLE CAUSE OF HEART FAILURE

By WILLIAM B. LIKOFF, M.D.

AND

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ONE of the most brilliant advances in the modern treatment of heart disease concerns the small but significant group of thyrocardiacs. As a result of increased diagnostic facilities, the great improvement in preoperative medical care, and the advances in surgical technique, many patients suffering from even advanced congestive heart failure or incapacitating angina pectoris are restored to good health when they are found to have thyrotoxicosis. The general dictum that under proper care no thyrocardiac is too sick to be operated upon is almost literally true. It must be appreciated that these cases are peculiar, in that the ordinary measures employed in the treatment of heart failure prove ineffective and improvement and recovery only take place when the underlying burden of thyrotoxicosis is removed. In that sense they constitute possibly the largest group of so-called curable or reversible heart disease. Numerous publications have appeared during the past two decades emphasizing the importance of recognizing the less obvious of these cases which have been called

"masked thyrocardiacs." Despite this great interest, fairly competent physicians still overlook these cases for many months or years, permitting invalidism to continue that is entirely unnecessary.

One of the practical difficulties in this problem is that when the obvious evidence of hyperthyroidism (exophthalmos and thyroid enlargement) is absent these patients have the symptoms and signs of heart failure similar to those that are commonly met with in general practice in patients who have no hyperthyroidism. In other words they are not unlike those who have hypertensive heart disease, coronary artery disease, rheumatic valvular disease, or any other common form of heart disease. The difficulty is increased because of the fact that most thyrocardiacs with heart failure also have these additional burdens on the circulation. The result is they are treated for valvular disease, coronary artery disease, or hypertensive heart failure (which they often have) and the additional thyrotoxicosis is entirely overlooked. Finally, thyrotoxicosis *per se* may produce signs and symptoms which closely simulate those found in mitral stenosis.[7] Under such circumstances, the physician may treat a case for mitral stenosis when no such lesion is present and when the entire illness is due to "masked hyperthyroidism." The methods employed in detecting "masked hyperthyroidism" have been adequately discussed in the past[5] and will not be taken up here.

It has long been known that when hyperthyroidism is associated with heart failure there is almost always some other independent type of heart disease. In fact, this has been so common and so striking that some authorities would lead us to believe that thyrotoxicosis alone never produces heart failure.[6] To be sure, one is frequently impressed by instances in which a thyrotoxic state has persisted for many years without any failure. However, there have been reported cases of heart failure in which no other etiologic factor could be detected except hyperthyroidism.[5] Some investigators are tempted to explain these latter cases on the basis that heart failure occurs because of unrecognized coronary artery disease, myocardial fibrosis, or other senile changes.[4] It is the purpose of this paper to offer clinical evidence indicating that thyrotoxicosis can be the sole cause of congestive heart failure.

All cases with thyrotoxicosis in which a subtotal thyroidectomy was performed at the Peter Bent Brigham Hospital between 1923 and 1941, inclusive, were analyzed in this study (Table 1). All those regarded as having increased thyroid function whether as a part of diffuse hyperplasia or toxic adenoma were included. There were 409 such cases, 314 females and 95 males, a proportion of more than 3 to 1. These were divided into two groups: "non-cardiacs" (331 or 81%) and "cardiacs" (78 or 19%). The former consisted of those instances in which no other type of heart disease, apart from thyrotoxicosis, existed. The latter 78 cases included 45 with hypertensive heart disease (the blood pressure being found above 150/90 on repeated examinations), 20 with definite rheumatic valvular disease, 12 with either angina pectoris or coronary thrombosis, and one with syphilitic

aortic insufficiency. Further analysis showed that 4 of the rheumatics and 8 of the coronary cases had hypertension in addition, indicating that there really were 57 cases with hypertension. It also may be added that 2 with rheumatic heart disease had definite angina, increasing the total of the coronary group to 14. It is obvious that independent organic heart disease is not uncommon in patients with thyrotoxicosis. The large number (5% of the entire 409) with rheumatic valvular disease is particularly impressive, for the expected incidence of rheumatic heart disease in the population of this community is no more than 1% to 2%.

TABLE 1.—THYROTOXICOSIS WITH SUBTOTAL THYROIDECTOMY
(PETER BENT BRIGHAM HOSPITAL, 1923–41)

	No. of patients	Females	Males	Average age (yr.)	Average duration of thyrotoxicosis (mo.)	Auricular fibrillation
"Non-cardiacs":						
Compensated	310	240	70	40	8	22
Decompensated	21	19	2	44	29	8
Severe	8	7	1	45	55	7
Moderate	13	12	1	43	12	1
Total	331	259	72	40	9	30
"Cardiacs":						
Compensated	39	28	11	53	7	6
Decompensated	39	32	7	52	10	23
Severe	23	19	4	52	9	20
Moderate	16	13	3	52	11	3
Total	78	60	18	53	8	29
Hypertensives:						
Compensated	27	19	8	54	8	5
Decompensated	18	15	3	57	11	8
Total	45	34	11	55	9	13
Coronary artery disease:						
Compensated	8	5	3	56	7	1
Decompensated	4	4	0	61	10	3
Total	12	9	3	58	8	4
Rheumatic heart disease:						
Compensated	4	4	0	43	6	0
Decompensated	16	13	3	44	8	12
Total	20	17	3	44	8	12
Luetic heart disease	1	0	1	52	8	0
Grand total	409	319	90	42	9	59

Of greater interest was the occurrence of congestive heart failure. By this term is meant the appearance of objective evidence of congestion, such as pulmonary râles, hydrothorax, enlarged liver, and peripheral edema in addition to the subjective complaints of dyspnea, cough, palpitation, and weakness. Patients having only subjective symptoms such as palpitation (even if auricular fibrillation were present), or breathlessness, and those showing definite cardiac enlargement, but without the objective signs enumerated above, were not regarded as having heart failure for purposes of this study. The history of swelling of the feet was very common in this group, but was not sufficient to classify the case as having heart failure unless pitting edema was observed in the hospital. The degree of heart failure was

further divided into two groups, severe and moderate. The former had definite hydrothorax or large palpable liver (generally both), with or without ascites, while the latter had significant pitting edema, râles at bases of lungs, in addition to the symptoms of myocardial insufficiency.

Among the 78 cases of thyrotoxicosis having some additional form of organic heart disease, there were 23 with severe and 16 with moderate congestive heart failure (50%). What is more significant is that in the "non-cardiac" group (331 cases) there were 8 with severe and 13 with moderate failure (6.3%). These latter 21 cases supply the main evidence that thyrotoxicosis alone may cause heart failure even when the blood pressure, the coronary arteries, and the valves are normal. The following case history is a striking example.

H.W. (M. 58597) female, age 34, entered P.B.B.H. December 19, 1940. There was no past history of rheumatic fever or chorea. She was apparently well, though slightly tired, until December, 1939. She then had "intestinal flu," with some nausea and diarrhea, and was in bed about 6 weeks. After this she first noticed shortness of breath, but was able to carry on. In June, 1940, she first noted a rapid, irregular beating of the heart, a generalized erythematous rash, and marked increase in breathlessness. She had been in bed off and on ever since. On several occasions fluid was removed from her right chest by tapping. The appetite had been good most of the time. During recent weeks there was some swelling of abdomen, ankles, right arm, and right side of face (patient had been lying on right side most of the time).

Physical Examination. Patient seemed to be acutely sick. There were numerous punched-out, crusting, erythematous pustules all over her body. Almost the entire right chest was flat with diminished breath sounds. The apex impulse was felt at the left anterior axillary line. The rhythm was grossly irregular, and the sounds hyperactive. There was a Grade II apical systolic murmur, but no diastolic murmur could be heard. The blood pressure was 130/60. The cervical veins were moderately distended. The liver extended a hand's breadth below the costal margin and there was moderate ascites. There was some pitting of the sacrum but not of the legs.

The first impression here was that we were dealing with a case of mitral stenosis and auricular fibrillation. This diagnosis was supported by the finding of marked right axis deviation in the electrocardiograms and a dilatation of the left auricle on fluoroscopic examination. Further studies, however, seemed to point more and more to diagnosis of hyperthyroidism. The velocity of blood flow was found to be 14 seconds. The B.M.R. ranged between +33 and +47. Venous pressure was 175 mm. Vital capacity was 500 to 800 cc. The urine and blood were not abnormal. Although there was considerable doubt as to the diagnosis in the minds of many physicians who saw her, as there was no exophthalmos or definite thyroid enlargement, she was given Lugol's solution and otherwise continued on the same cardiac management as before, i. e., digitalis, mercupurin, and chest taps. She gradually improved, although she still had a considerable hydrothorax. The B.M.R. fell to +12. A one-stage subtotal thyroidectomy was performed January 13, 1941. Pathologic examination of the gland showed diffuse hyperplasia with iodine involution. She continued to improve in an amazing fashion. Because the auricular fibrillation persisted she was given quinidine on January 23, and after a few doses of 0.3 gm., the rhythm became regular. Right axis deviation persisted in the electrocardiograms. The postoperative B.M.R. was +2? Recovery thereafter was complete so that now, 2 years after operation, the patient is perfectly well doing full duties as a housewife, and has no signs or symptoms of heart disease.

Analysis of the *sex* relationship among these patients reveals the fact that women bear thyrotoxicosis less well than men. It was found that while the proportion of female to male among those who did not have heart failure in the "non-cardiac" group (310 cases) was $3\frac{1}{2}$ to 1, the proportion for those who went into failure was 10 to 1 in favor of females. The corresponding figures for the 78 cases belonging to the "cardiac" group were $2\frac{1}{2}$ to 1 for those without heart failure and $4\frac{1}{2}$ to 1 for those with failure. It is not clear from this study why women are more likely to have heart failure as a result of hyperthyroidism.

It is to be expected that *age* would play a rôle in determining the development of congestive failure. Older patients might have undetected degenerative changes in the myocardium more frequently and are also more likely to have had the thyrotoxic state for a longer time. This is borne out by the fact that patients with coronary artery disease and congestive failure were on the average 5 years older (61 years) than those without failure (56 years). Likewise, the hypertensives were 3 years older on the average (57 years) when congestive failure was present than when absent (54 years). Even the thyrotoxic patients without other etiologic types of heart disease were 4 years older (44 years) when congestive failure was present than when absent (40 years). It must not be inferred, however, that heart failure from thyrotoxicosis can occur only in the aged. In this study there were 6 instances of congestive heart failure in patients under the age of 40, and 3 under the age of 30 when there was absolutely no evidence of other lesions such as rheumatic valvular disease, hypertension, or coronary artery disease.

Another possible factor in the production of heart failure might well be the *duration* of thyrotoxicosis. It would seem that the longer the deleterious effect of hyperthyroidism might continue the more likely the heart would fail. It was not a simple matter to analyze this point, as often the onset of thyrotoxicosis could be determined only with difficulty. It is of interest, however, that the duration of thyrotoxicosis in the "non-cardiac" group with severe failure was 55 months, with moderate failure 12 months, and with no failure 8 months. It was to be expected that heart failure would result sooner in those already having organic heart disease. This proved to be the case, for the duration of thyrotoxicosis in the "cardiac" group with failure was only 10 months. The important inference is that if thyrotoxicosis remains uncontrolled for years it may eventually produce heart failure even if there is no preëxisting heart disease.

It has long been known that *auricular fibrillation*, either paroxysmal or permanent, is frequently a part of the clinical picture of thyrotoxicosis. The paroxysmal form is common, particularly directly after the operation, in cases showing very little evidence of cardiac involvement and no evidence whatever of heart failure. Permanent fibrillation, however, is much more likely to be associated with other types of heart disease or severe heart failure. In this present analysis only cases known to have permanent fibrillation were considered. It is of interest that among 78 cases belonging to the "cardiac" group there

were 23 with severe heart failure of which 20 were fibrillating, and 16
with moderate failure of which 3 were fibrillating. Among the 20 with
rheumatic heart disease, 16 were in failure of which 12 had auricular
fibrillation, and the 4 who were compensated all had a normal rhythm.
Among the 57 cases with hypertension or coronary artery disease,
22 were in failure of which 11 had auricular fibrillation, and 35 were
compensated, 6 having auricular fibrillation. In contrast to the
"cardiac" group, there were 331 "non-cardiac" cases of which 21
were decompensated. Eight were in severe failure, 7 of which were
fibrillating, and 13 were in moderate failure, only 1 of which was
fibrillating. Of the 310 who were compensated, 22 were fibrillating.
It follows that if congestive failure is present, fibrillation will be very
frequent in the rheumatic group, less common in the hypertensive
and coronary group, and least frequent in the "non-cardiac" group.
Furthermore, when fibrillation does occur in a rheumatic case one
may expect that failure will always be present; when this arrhythmia
accompanies hypertension or coronary artery disease, decompensation
will be expected in 65% of the instances, and when it is found in a
"non-cardiac" case of hyperthyroidism the incidence of failure is 27%.
The close relationship between auricular fibrillation and heart failure
is also apparent in the following figures. The incidence of auricular
fibrillation in the "non-cardiac" group without failure was 7%,
while with failure it was 38%. The incidence in the "cardiac" group
without failure was 15%, and with failure 59%. The irregularity,
therefore, was 4 or 5 times as frequent when heart failure was present
than when it was not. It was even more frequent in the presence of
heart failure in those having no organic heart disease than in those
having independent heart disease but no congestive failure.

The similarity between mitral stenosis and thyrotoxicosis has already
been mentioned. Both conditions obviously are accompanied by
symptoms of cardiac disability, such as dyspnea, palpitation, weakness,
and congestive failure, and both conditions may present similar find-
ings on physical examination, i. e., cardiac enlargement, transient or
permanent fibrillation, accentuation of first heart sound, systolic
murmurs, and slight apical thrill. To be sure, the thrill in mitral stenosis
is presystolic and in hyperthyroidism is systolic, but when the heart
rate is rapid it is often impossible to make this distinction on palpation.
The one distinguishing point is the diastolic murmur which does not
occur with thyrotoxicosis. On the other hand, this tell-tale sign may
be absent in mitral stenosis in some cases, or inaudible when the rate
is rapid. The great frequency of the coëxistence of mitral stenosis and
thyrotoxicosis may further complicate the diagnostic problem.

The additional point we wish to make at this time is that the Roent-
gen ray evidence of mitral stenosis may also add to the confusion. It
is well-known that enlargement of the left auricle especially posteriorly
is a very early and valuable sign of mitral stenosis. Some enlargement
of the left auricle was observed in 8 of 17 cases in this series that had
heart failure from thyrotoxicosis per se. Although this left auricular
enlargement was not very marked, it was no less in degree than many

cases of early mitral stenosis show and sufficient to suggest mitral disease from a roentgenologic point of view.   Enlargement of the pulmonary artery has been noted by Parkinson and Cookson,[11] but no mention was made of a similar enlargement of the left auricle. The fact that this left auricular dilatation is a part of the thyrotoxicosis is confirmed by the observations made in these instances after the metabolism had returned to normal and cardiac compensation reëstablished. Five cases that had shown dilatation of the left auricle on fluoroscopic examination preoperatively failed to show this change postoperatively. It might be thought that the fibrillating state of the auricles rather than the hyperthyroidism caused the slight dilatation of the left auricle. That this is not the case is borne out by the fact that left auricular dilatation was found in some cases with a regular rhythm and was observed to decrease in extent after operation when the metabolism was normal even while fibrillation continued. It follows, therefore, that dilatation of the left auricle in some cases is a specific result of thyrotoxicosis.

Discussion.   It is abundantly clear from an analysis of the cases in this study that congestive heart failure of a mild or even of extreme degree can result from thyrotoxicosis when careful search fails to reveal any of the other common etiologic causes of heart disease such as valvular disease, hypertension, or coronary sclerosis.   Although this has been noted by other observers, its importance and frequency has not been sufficiently emphasized. In fact, the frequent finding of these other forms of heart disease in patients with hyperthyroidism who have congestive failure has led to the view that hyperthyroidism alone does not produce heart failure. This prevailing opinion is particularly unfortunate because it tends to make physicians overlook this small but important group of thyrocardiacs in which heart disease is actually curable or reversible. When the obvious evidence of thyrotoxicosis such as exophthalmos and thyroid enlargement is not present, one is too ready to regard these patients as having incurable heart failure from mitral stenosis, myocardial degeneration, hypertension, or coronary artery disease when none of these complications is present. One might add that even if they were present, it still is extremely important to discover the added burden of thyrotoxicosis, for the latter can be removed whereas the former cannot.

If one still had doubt concerning the absence of other forms of heart disease in the group of 21 cases that had congestive failure from thyrotoxicosis alone, it can be dispelled by the evidence furnished from the follow-up study. After an average period of 5 years (the longest was 10 years), none of these patients showed any evidence of organic heart disease. There were 4 deaths during this period, all from carcinoma. All the others were essentially well.

It is difficult to explain the mechanism of heart failure when it is the sole result of thyrotoxicosis. It is obvious that hyperthyroidism can continue for years in some cases without producing heart failure. Is it purely the result of increased work? Obviously there is increased work of the heart that continues even with the patient at rest when the

basal metabolic rate is abnormally elevated. It is difficult to believe that this is the only factor involved. Is there a specific or non-specific toxic factor that injures the myocardium? There are rare reported examples of focal myocardial necrosis associated with hyperthyroidism.[?] The auricular fibrillation so common in hyperthyroidism may well be looked upon as a toxic manifestation, for the arrhythmia may even precede the elevation in the basal metabolism. Once auricular fibrillation has developed, it can be an added factor in the causation of heart failure, for prolonged uncontrolled auricular fibrillation in an otherwise normal heart may result in heart failure.[1,9] Finally, one cannot escape the similarity between some of the clinical features seen in heart failure from beriberi disease and thyrotoxicosis. Several years ago Soma Weiss suggested that some of the features of thyrotoxicosis could well be due to vitamin B deficiency.[13] A similar view has been held by Means.[10] This possibility was not investigated in this study although during the past few years, since the importance of vitamins has been more fully appreciated clinical evidence of deficiency states, such as red palms and sore, smooth, red tongue has been repeatedly observed in these thyrocardiacs. This whole subject is quite important and deserves further study. It probably will be found that cases of hyperthyroidism with heart failure will show much more chemical and clinical evidence of vitamin deficiency (especially the B complex) than those without heart failure. If this concept is correct it ought to be true that with the same metabolic rate, thyrotoxic patients with heart failure will be found to have had a poorer appetite, and to have taken a poorer diet, than those without heart failure.

There is another practical consideration with regard to the surgical treatment of these patients that seems important. At first glance one might feel that these severe thyrocardiacs, having not only thyrotoxicosis but advanced heart failure, would prove to be the most difficult and the most serious from a surgical point of view. In fact, this view is so current that many physicians and surgeons advise multiple stage operations for such severe cases.[6] We have had quite the contrary view in this clinic. It has been our impression that the operative mortality and incidence of alarming thyroid storms have been no more or even less in the older, severe thyrocardiacs than in the younger cases of exophthalmic goiter. This was borne out by the following analysis: There were no instances of thyroid crisis among the 60 patients who had heart failure, while of the remaining 349 that had no heart failure, 18 developed a thyroid storm. Even more important were the differences in the operative mortality. There were 8 deaths in 310 cases showing no evidence of heart disease or heart failure (2.6%). In contrast there were no fatalities among 21 "non-cardiacs" with heart failure, and 78 cardiacs, half of whom had heart failure.[*] It is difficult to explain the discrepancy between the absence

* One of these latter cases was literally moribund and unconscious at the time of operation, which was performed as an emergency procedure for an intrathoracic goiter. The surgeon feared the patient would not leave the operating room alive if not operated upon. He died 1 hour postoperatively.

of any operative mortality in this latter group and the occurrence of 4% mortality among thyrocardiacs in the Lahey Clinic as reported by Hurxthal.[4]   The outstanding impression we have had is that the severe thyrocardiac never worries us before, during or after the operation.   It is the younger individual with classical Graves' disease that may suddenly develop a severe or even fatal crisis.   Furthermore, it is not without significance that all but 7 cases had one-stage operations. This is also in conflict with the prevailing teaching.[4,12]   If multiple stage operations are necessary in thyroid surgery, they do not appear to be indicated in the group of cases under consideration that show heart disease or heart failure.

Summary and Conclusions.   1. A study was made of 409 cases of thyrotoxicosis operated upon at the Peter Bent Brigham Hospital from 1923 to 1941, inclusive.   There were 331 (81%) "non-cardiacs" and 78 (19%) "cardiacs."   Among the latter there were 45 with hypertensive disease, 20 with rheumatic heart disease, 12 with coronary artery disease, and one with syphilitic aortic insufficiency.

2. There were 39 cases of heart failure among the 78 "cardiacs" (50%), and 21 instances of definite congestive failure among the 331 "non-cardiacs" (6.3%).   It is apparent, therefore, that thyrotoxicosis not infrequently is the sole cause of congestive heart failure.

3. It was found that congestive failure was more likely to occur in the female sex, with increasing age, when the thyrotoxic state lasted longer, and when auricular fibrillation was present.   No satisfactory explanation was found for the heart failure especially in the "non-cardiac" group.   It is suggested that vitamin B deficiency may play a contributory part.

4. The similarity between symptoms and physical findings in mitral stenosis and thyrotoxicosis may lead to errors in diagnosis, for even left auricular dilatation on Roentgen ray examination is found in the latter condition.

5. In 99 cases with cardiac involvement there was no surgical mortality.   All but 7 of these had a one-stage subtotal thyroidectomy. The surgical mortality in 310 cases without heart disease, however, was 2.6%.   We, therefore, do not believe that the so-called severe thyrocardiacs require a multiple stage operation, and feel that they cause less concern than the younger exophthalmic goiter when surgical treatment is planned.

6. It is evident that "masked thyrotoxicosis" is being overlooked as a cause of heart failure, an error which is very costly because the condition is curable.

REFERENCES

1. Brill, I. C.:   Am. Heart J., 13, 175, 1937.
2. Goodpasture, E. W.:   J. Am. Med. Assn., 76, 1545, 1921.
3. Hurxthal, L. M.:   Am. Heart J., 4, 103, 1928.
4. Hurxthal, L. M.:   The Thyrocardiac, Frank Howard Lahey Birthday Volume, Springfield, Ill., Charles C Thomas, 1940.
5. Kepler, E. J., and Barnes, A. R.:   Am. Heart J., 8, 102, 1932.
6. Lahey, F. H.:   Surg. Clin. North America, 14, 1225, 1934.
7. Levine, S. A., and Sturgis, C. C.:   Boston Med. and Surg. J., 190, 233, 1924.
8. Levine, S. A., and Walker, G. L.:   New England J. Med., 201, 1021, 1929.

9. LEVINE, S. A., and BEESON, P. B.: Am. Heart J., 22, 401, 1941.
10. MEANS, J. H., and LERMAN, J.: Ann. Int. Med., 11, 429, 1937.
11. PARKINSON, J., and COOKSON, H.: Quart. J. Med., 24, 499, 1931.
12. TINKER, M. B., and TINKER, M. B., JR.: Trans. Am. Assn. Study Goiter, p. 75, 1941.
13. WEISS, S., and WILKINS, R. W.: Trans. Assn. Am. Phys., 51, 341, 1936.

THE CONTROL OF POLYCYTHEMIA VERA BY VENESECTION

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PATIENTS with polycythemia vera usually obtain symptomatic relief from measures which reduce the excess of circulating erythrocytes. The excess may be destroyed by phenylhydrazine, removed by venesection or reduced by the suppression of bone marrow activity from
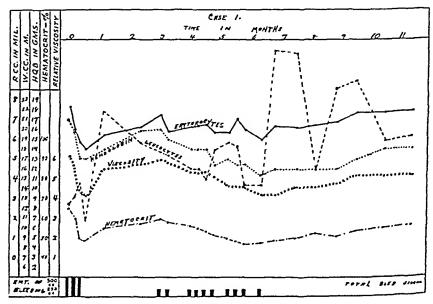
FIG. 1.—Changes in blood findings.

Roentgen irradiation or other injectable irradiated elements. The use of irradiation and phenylhydrazine has been criticized because the destructive power of the agent cannot always be completely controlled. In spite of this potential danger irradiation in one form or another is the most widely used method of treatment. The commonly accepted view that venesection is not wholly satisfactory for this disease is expressed by Harrop[1] as follows: "One must conclude that while

venesection is an important and useful relief in emergency in the treatment of these patients. it cannot be looked upon in any other light
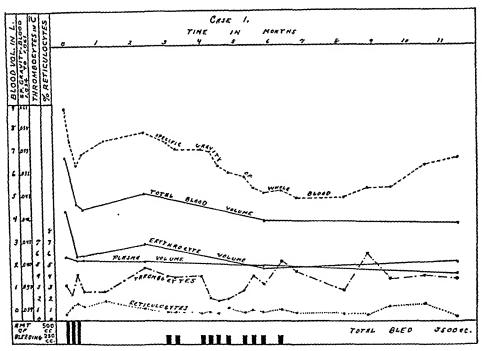
FIG. 2.—Changes in blood findings.
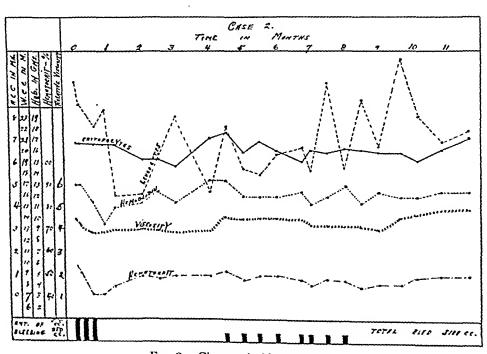
FIG. 3.—Changes in blood findings.

than as a further and therefore undesirable stimulant to new blood formation."

The difficulty in evaluating therapy of any disease is accentuated in

the case of polycythemia vera because spontaneous changes occur normally. Rosenthal and Bassen[2] have recorded a variety of stages and unusual manifestations such as symptomless periods, spontaneous development of anemia, periods with great leukoblastic activity or with thrombocythemia. Despite such obstacles for accurate inter-
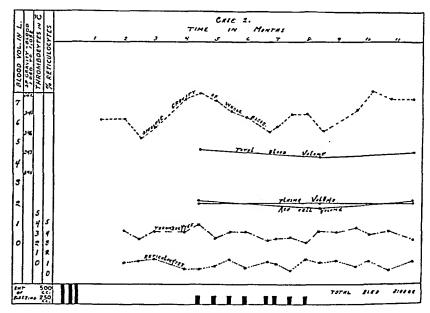
Fig. 4.—Changes in blood findings.
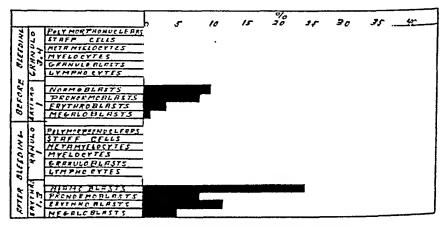
Fig. 5.—Differential bone marrow puncture—Case 1.

pretation a detailed study of two patients for more than a year suggests that venesection, properly used, is a safe method for adequately controlling the disease.

Hemoglobin was studied by the Sahli method; blood and plasma volume by the Evans blue method; blood and plasma viscosity with a

Hess viscosimeter and specific gravity of whole blood and plasma by the falling drop method. For hematocrit estimations heparin was the anticoagulant. In both cases the diagnosis of polycythemia vera was confirmed by computing the volume of circulating erythrocytes. By estimating the excess over normal it was possible to calculate the approximate amount of blood to be removed.

At first an attempt was made to eliminate the excess quickly by removing as much as 1500 cc. in a 14 day period. This produced a marked fall in erythrocyte volume, hemoglobin, specific gravity and viscosity. Partial symptomatic relief of certain symptoms (tingling of fingers, fullness in the head and generalized aching) was obtained, but undesirable symptoms were also produced. Evidence of erythropoietic stimulation (slight rise in reticulocytes and changes in bone marrow cytology) added to unwanted effects. Then we decided to study the effects of removing smaller amounts at intervals of about 2 weeks. By using a syringe of 100 cc. capacity that contained 5 cc. of sodium citrate solution, 200 to 250 cc. could be removed as simply as any other office procedure. At once we found that no symptoms were produced by small venesections. Figures 1 to 4 record the changes in blood findings over a 12 month period and allow a comparison of the effects produced by the two methods. When the small venesection was employed there was a gradual reduction of hematocrit values, blood viscosity, and hemoglobin. This effect was in sharp contrast to that produced by the large venesection in which a sharp fall was followed by an equally steep rise. After repeated small venesections it was observed that the fall in hemoglobin was not equaled by a corresponding fall in numbers of circulating red cells, because the latter had become microcytic. When the computed excess had been removed, bleedings were discontinued. For several weeks the patients remained asymptomatic with only slight developments toward an erythremic state. Four months after cessation of bleeding in Case 2, and 5 months after in Case 1, the return of symptoms was associated with rise in hemoglobin and erythrocyte volume. Again a series of small bleedings was instituted. In both cases spleen size was reduced by removal of blood and became larger when erythrocyte volume rose. In this disease it is obvious that an estimation of erythrocyte volume is the best guide for therapeutic need. Technical difficulties prevent widespread repeated use. It appears that a hematocrit reading alone with hemoglobin estimations and erythrocyte counts serves as an adequate substitute. Blood viscosity or specific gravity determinations offer no advantages, either of accuracy or simplicity.

Conclusions. The following method for the control of symptoms of polycythemia vera is suggested: To determine the actual excess of circulating erythrocytes as well as confirm the diagnosis, an estimation of the total erythrocyte volume is made; at weekly or bimonthly intervals 200 to 250 cc. of blood is removed by venesection; this may be carried out in the office by using 100 cc. syringes; the bleedings are continued until the computed excess of erythrocytes is removed or until hematocrit, hemoglobin and erythrocyte counts reveal beginning

anemia; bimonthly estimations of hemoglobin, erythrocyte counts and hematocrit will detect recurrence of the erythremic state and point out the need for further venesections. Two patients treated by this method for more than a year have remained free from symptoms.

REFERENCES

1. HARROP, G. A., JR.: Medicine, 7, 291, 1928.
2. ROSENTHAL, N. J., and BASSEN, F.: Arch. Int. Med., 62, 903, 1938.

OBJECTIVE METHODS TO DETERMINE THE SPEED OF BLOOD FLOW AND THEIR RESULTS (FLUORESCEIN AND ACETYLENE)*

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THE determination of velocity of blood flow has gained a definite place in the examination of cardiac patients and in those with endocrine disturbances or pulmonary disorders which impair the flow of blood through the lungs. If this diagnostic procedure has not yet found general adoption, it is mainly because the available methods were either subjective and thereby carried a certain intrinsic fraction of unreliability or, when objective, the complicated apparatus required considerable laboratory facilities. Furthermore, the subjective method fails precisely in those cases where the determination of the circulation time has decisive value, namely in unconscious patients and in children with congenital heart diseases. Moreover, the subjective factor implicit in many methods is responsible for some of the dubious results obtained and tends to discredit the basic valid conception itself. Finally, some methods in use were not free from danger. Fatalities and serious complications after the determination of circulation time have been reported and have further discredited these methods.[6,14]

The inhalation of carbon dioxide by the method of Bornstein[1] belongs, to some extent, among the objective procedures. However, the threshold of response in the centers involved may be quite different individually and, as Berliner[2] has shown, may vary even in the same person under different conditions. Furthermore, it necessitates considerable equipment and is scarcely applicable in children and in unconscious patients.

The lobeline method fails to evoke a response in all patients, and is subject to the same criticism. The same objection holds for the sodium cyanide method; in addition it may cause syncope and respiratory arrest.[17]

The use of radioactive substances[4] requires rather elaborate equipment and is not free of danger. The histamine method[12] is also not

devoid of danger, as the authors state themselves. It also is apt to fail in certain individuals, especially when lung pathology is present.

Koch[11] was the first to use fluorescein for the determination of the speed of blood flow. He injected it into the antecubital vein of one arm and withdrew blood from the other arm, taking a specimen every 5 seconds and watching for the first appearance of luminescence in full daylight. This method, although harmless, is rather inaccurate and somewhat complicated.

In 1931, Lange and Wollheim[20] demonstrated that an adequate source of light makes fluorescein emit a luminescence sufficiently strong to be seen in human vessels of small caliber. However, the available sources of light required for such an examination were somewhat clumsy and not readily applicable in general practice. Since that time we have simplified the method that it can now be considered practical for general use.

The appearance of the fluorescein can also be observed in all parts of the intestine when the peritoneal cavity is opened as well as in the skin of the entire body to give objective information about peripheral vascular diseases and inflammatory reactions.[10,12]

In a circulation-time test one determines the speed of blood flowing fastest in the axis of the vessel from the point of injection to the point of observation. Since the estimation is made in a single segment of the circulation the result does not necessarily obtain for the entire vascular system, because different conditions may prevail in another circuit. Accordingly, it must be proven under conditions in which the circulation in one single circuit is not especially rapid or slow that the determination of the circulation time, gives an exact picture of the average circulation time. To avoid the mistake of employing an abnormal circuit, 5 conditions must be fulfilled: (1) The circuit must contain all essential parts of the circulatory apparatus, that is, a vein, the pulmonary circulation, an artery, arteriole and capillary. (2) The circuit must be at basal conditions for the given individual; it must not have abnormally dilated arterioles or capillaries created by purely local factors. (3) The point of observation should permit the detection of the arrival of the test substance in the capillaries and not in the smaller arteries or arterioles. (4) The quantity of material injected must be sufficiently large to require several contractions of the heart for ejection in order to avoid any mistake created by the material passing the point of examination without detection on its first passage or being shunted into unobserved circuits by abnormal stream conditions. (5) The injected material should not influence the velocity of blood flow.

Very recently, Fishback[7] and his associates modified our original method; in place of using the lips as a point for observing the appearance of the fluorescein they chose the conjunctiva and the sclera. Under these circumstances, the conditions (2) and (3) mentioned above are not fulfilled. According to Mueller and Laube[13,15] the vessels of the conjunctiva are extremely sensitive to touch and dilate readily, and all types of vessels (small arteries, arterioles, capillaries and

venules) can be easily observed and hardly distinguished from each other without recourse to a capillary microscope. This may explain the wide variations of values obtained by these observers. Moreover the direction of the ultraviolet light to the eyes causes some discomfort and this factor alone may change the vascular status. The retraction of the eyelids required by this modification certainly changes the local vascular status.

Nature of Fluorescein. Fluorescein is resorcinophthalein. It is readily available, inexpensive and non-toxic. One gram has been given orally as a test of renal function without any deleterious effects;[13] as much as 6 gm. have been given by the same route to stain certain parts of the eye; no untoward symptoms follow although the skin may be stained yellow for 12 to 30 hours under these circumstances.[9] Fluorescein undergoes no change in the body and is rapidly excreted in the urine. In over 600 injections we have given so far we had 3 instances of slight nausea for about 1 minute. In these 3 cases, 10 cc. of the fluorescein solution were injected too rapidly intravenously since peripheral vascular studies were intended.

When examining the physical properties of fluorescein for possible use as a vital stain, we found its strongest fluorescence is emitted when the source of light has a wave length of 3600 to 3800 Angström units; this is the region of long wave ultraviolet. This deep purple light causes fluorescein to emit a golden or green luminescence depending upon the hydrogen-ion concentration of the media in which the action takes place. In an acid solution the emitted light is yellow; in an alkaline solution it is dull green. To secure the greatest possible contrast, the source of light should exclude nearly all the visible light and all erythema producing ultraviolet. The characteristics of a suitable filter is shown in Figure 1.

Method for Testing the Fastest Circulation Time by Means of Fluorescein. A special, small, inexpensive mercury vapor bulb with a concentrated light beam (Fig. 2) is provided with a purple glass filter which absorbs all the harmful ultraviolet and most of the visible rays.* Of the emitted light 65% is transmitted at the wave length of 3600 Angström units. The beam of this concentrated light is directed against the lips of the patient. The examination should take place, if possible, in a dark room; 5 cc. of a 5% fluorescein solution containing 5% of sodium bicarbonate are injected rapidly by means of a 20 gauge needle into the antecubital vein of the adult patient. Solutions of *sodium* fluorescein in adequate amounts[7,8,11] is optically much less effective and has no advantages over the solution of fluorescein with sodium bicarbonate.† In children 0.7 cc. of solution per 10 kg. of body weight is injected. After the circulation time has passed, the part under observation (lips) suddenly acquires a greenish yellow hue. This end-point is very sharply defined. When several observers are present they rarely disagree by more than 1 second on the moment it appears. If a subsequent examination is intended within a short period, the dose for adults may be cut down to 3 cc. Within 15 minutes the effect has been sufficiently diminished to permit a second examination with a clear cut result.

Normals. Two hundred and sixteen adults from 19 to 95 years of age who never had had any signs of cardiac failure were examined with

this method. Great care was taken that all cases were under basal conditions; before the test was made they rested for at least 15 minutes when bedridden, or 30 minutes when ambulatory. However, no fasting
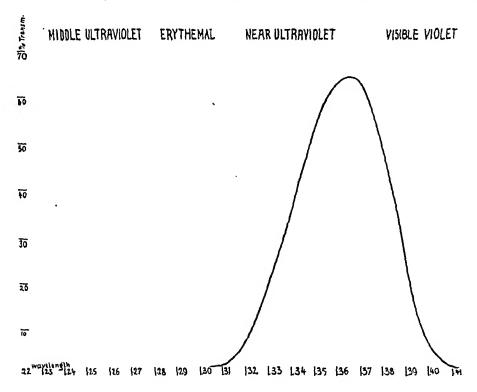
FIG. 1.—Transmission characteristic of the filter as used for the fluorescein observations. A double filter was used in order to decrease transmission of visible light.
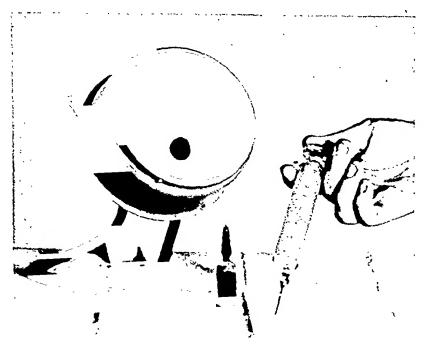
FIG. 2.—Devices needed for the fluorescein test.

was requested. Since many (108) of our patients were elderly, peripheral vascular disease such as arteriosclerosis was not uncommon. In these patients 10 cc. of the fluorescein solution were used in order to observe the status of the peripheral circulation simultaneously. The values ranged almost exclusively between 15 and 20 seconds. The moment at which *full* luminescence appeared in the lips was taken as end-point in all cases. Figure 3 gives the distribution of the values found. It is evident that the great majority of cases ranged around 15 to 17½ seconds; however, if one studies Tables 1 and 2 in which the normals
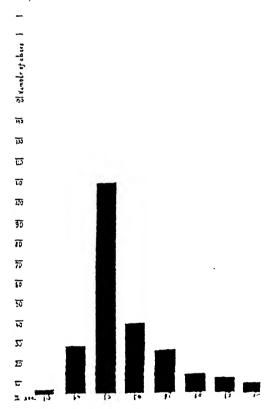
Fig. 3. - Distribution of cases within normal range for circulation time.

are distributed by age, it becomes evident that there is a definite trend toward slower circulation time with increasing age. If repeated tests were done on the same patient at short intervals, the values never differed more than 3 seconds; in the majority the difference was 2 seconds or less (Table 4).

Effect of Exercise. Work causes considerable acceleration of the circulation time. The highest value was 6 seconds with maximal exertion of 1350 mkg./min., which could be performed only for a few minutes; this individual had a circulation time of 15 seconds at rest. Moreover, the arm-lip circuit is not the one actually subjected to maximal vasodilatation from exertion; some of its parts may even undergo contraction to make blood available for the working muscle. Therefore this method should not be considered a correct measurement of the relative increase in cardiac output under exertion. The acetylene method, described below, tends to provide an exact impression of the actual average increase in blood velocity under such extreme conditions.

TABLE 2.—DISTRIBUTION OF CASES IN THE DIFFERENT AGE GROUPS ACCORDING TO THEIR CIRCULATION TIME

Circulation time (sec.)	Age group (yrs.)				
	20–30	30–40	40–50	50-70	Over 70
13–13.9	4				
14–14.9	18	5	2		
15–15.9	18	42	34	11	
16–16.9	4	1	21	9	
17–17.9	0	4	2	16	1
18–18.9	2	1	1	3	3
19–19 9	..	..	..	8	1
20–20.9	..	..	1	4	

Effects of Fever. Six otherwise normal patients were observed during pyrexia due to infectious diseases. The circulation time varied between 9 and 13 seconds whereby no direct relation between the increase in temperature and the percentage of acceleration of blood velocity could be discovered.

TABLE 3.—CIRCULATION TIME

No.	Clinical diagnosis	Arm-conjunctiva	Arm-lips	Arm-rectum	Arm-foot
1	Wound on rt. foot; duodenal ulcer	9	15	19	23
2	Laceration of rt. foot	11	15	20	22
3	Laceration of lt. foot; caisson disease	8	16	21	24
4	Laceration of lt. foot	8	16	20	23

Circulation Time to Different Points of the Body. In 4 patients the fluorescein circulation time was observed at 4 *different points* of the body after the same injections of fluorescein. All patients had a healing open lesion on the foot not due to arteriosclerosis, so that this district could be employed as one point of observation. The second point was the mucosa of the rectum, the third point was the lips, and the fourth the conjunctiva. Four mercury vapor lamps were used; each observer had made many observations previously and was fully acquainted with the method. The results are shown in Table 3. Here again the question arises as to whether the values obtained on the foot and the conjunctiva are more than an approximation of the true blood velocity to these regions.*

* After the conclusion of this paper a photoelectric method was developed to make circulation time determinations to any point of the body. Determinations with this fully automatic method using fluorescein have proved these values correct. In a normal the arm-leg time never exceeds twice the value obtained for the arm-lip time.

Bronchial and Cardiac Asthma. According to Plotz,[16] patients in an attack of pure bronchial asthma show a normal or slightly shortened circulation time. We had the opportunity to observe 5 cases of this kind, and could confirm these results objectively. In contrast to them, 3 cases of pure cardiac asthma (left and no right heart failure) showed a high normal or prolonged circulation time, the extremes being 32 and 20 seconds. Accordingly, the circulation time aids in making the differential diagnosis between these 2 kinds of "asthma" but only if one is dealing with a pure form. In 3 cases bronchial asthma was complicated by beginning heart failure in patients with a known cardiac lesion and slightly prolonged circulation time (22, 23 and 27 seconds) were found. However, prolonged circulation time in a suspected case of bronchial asthma seems to indicate that we are not dealing with a pure case and this fact has considerable importance in the therapeutic program.

TABLE 4.—TESTS REPEATED WITH INTERVALS

No.	Clinical diagnosis	Interval between both tests in min.	Seconds 1st test	Seconds 2d test
1	Decomp. mitral stenosis	60	32	30
2	Decomp. mitral stenosis	85	29	29
3	Decomp. aortic insufficiency	120	29	31
4	Decomp. hypertension	120	40	37
5	Decomp. hypertension	120	29	32
6	Decomp. aortic insufficiency	180	42	45
7	Decomp. mitral stenosis; auric. fibrill.	180	36	31
8	Decomp. hypertension	180	33	33
9	Decomp. aortic insufficiency; auric. fibrill.	180	38	42
10	Decomp. hypertension	180	48	44
11	Myxedema	120	24	24
11a	Same case	2 days	23	
		10 days	24	
		17 days	23	
		120 min. after previous test	24	
12	Normal	60	15	16
13	Normal	30	15	14
14	Hyperthyroidism	120	11	10
		1 day	12	
		2 days	10	

Hyperthyroidism. The average circulation time in 42 patients suffering from hyperthyroidism was 10.2 seconds: none of them showed a circulation time of more than 14 seconds and the shortest was 7 seconds. The circulation time seems to be a very sensitive test for hyperthyroidism and, in the absence of cardiac failure, it seems to correspond to the clinical picture much more closely than the basal metabolism rate. The circulation time may remain short after Lugol's solution and after operation even when the basal metabolism has returned to normal. Table 5 illustrates such a case.

Hypothyroidism. Ten cases of hypothyroidism were followed for a long time, and the circulation time was found slightly or markedly prolonged in all except one. The average in this group amounted to 26 seconds. The longest value was 32 seconds. With thyroid medication the values rapidly became normal only to return to slow circulation

times if the administration of thyroid was stopped. It was our impression that changes in circulation time occurred much earlier than changes in the clinical picture.

TABLE 5.—CIRCULATION TIME IN A CASE OF HYPERTHYROIDISM

Day of hospitalization	Treatment	Pulse rate	Basal metabolic rate	Circulation time (sec.)
3	Bed rest	116	+51	7
7	Bed rest	104	+48	8
17	Lugol's, 9 days	90	+32	10
24	Lugol's, 16 days	90	+19	10
25	Subtotal thyroidectomy			
32	Bed rest	96	+ 7	10
46	Out of bed	90	+ 4	11
69	At home	86	+ 4	16
90	At home	90	+ 6	16

Anemia. Twelve cases with anemia of various degrees were observed. Only those cases were included in which there was no other detectable cardiovascular disease. Table 6 seems to indicate that no apparent shortening of the circulation time appears until the red cell count falls to 3,500,000. Below this limit the heart compensated for the loss of oxygen carriers by increasing the speed of blood flow. The number of cases however, is insufficient to state definitely that 3,500,000 cells are tolerated without increase in circulation time.

TABLE 6.—CIRCULATION TIME WITH LOW RED BLOOD COUNT

No.	Clinical diagnosis	Erythrocytes (mill.)	Circulation time (sec.)	Erythrocytes (mill.)	Circulation time (sec.)
1	Pernic. anemia	1.3	9	2.9	12
2	Pernic. anemia	1.6	10	3 4	13
3	Bleeding duodenal ulcer	2.7	12		
4	Bleeding duodenal ulcer	2 6	12		
5	Cancer of stomach	2.5	10	2.3	10
6	Duodenal ulcer	3.0	13	2.4	11
7	Duodenal ulcer	3.2	13		
8	Duodenal ulcer	3 7	15	3.8	15
9	Bleeding hemorrhoids	3.8	16	4 5	16
10	Duodenal ulcer	3.9	15	4.3	16

Comparison Between Fastest and Slowest Circulation Time. To determine whether the fluorescein circulation time by this method is an exact measure of the blood flow in general, recourse was made to a procedure which provides certain information about the slowest flow and also about the average speed of blood flow. Acetylene was first used by Grollman[8a] to determine the stroke volume, but the circulation time can also be found by it. The gas is poorly soluble in the blood lipoids, but it is absorbed by the blood to saturation and can be exactly analyzed by relatively simple methods.

Method. The patient breathes a 6% acetylene-air mixture from a Douglas sack. The expired gas is separated and sufficient amounts are drawn into small rubber bags by Simonson's apparatus. Every 20 seconds a new bag is filled. The samples of gas thus received are then analyzed for their acetylene content. The percentage of acetylene gives the ordinate of a curve, the abscissa of which is represented by the time.

This method, originally devised by Baumann[1] for a different purpose, was used by us with our former collaborator Bielschowsky.[2] It yields information about the time which is required until no, or practically no, acetylene is absorbed by the blood. At this moment all blood has circulated at least once through the lungs. Under basal conditions, the saturation of acetylene in the expired air never fully reaches the values of the inspired gas mixture, since some acetylene diffuses into the tissue and some blood leaks into the rapid circulation from the blood depots. In normal individuals however, the curve becomes absolutely straight after $2\frac{1}{2}$ to $3\frac{1}{2}$ minutes, indicating that all blood in rapid circulation has passed at least once through the lungs. The slowest circulation time was observed in 24 normals in this manner. The same cases were examined with the fluorescein method and the values compared. By the acetylene method, the average for the slowest circulation time was 3 minutes.

Ten cases of thyrotoxicosis were examined the same way, as well as 13 cases of cardiac failure. The patients with thyrotoxicosis needed $1\frac{1}{2}$ to 2 minutes to reach the stabilized phase of the curve, the time varying in accordance with the severity of the disease. The figures obtained with this method agree very closely with those of the fluorescein method for the fastest circulation time.

Patients in cardiac failure had slowest circulation times between 4 and 6 minutes. Table 7 is a comparison between the values found with the fluorescein method for the fastest circulation time and the values found with the acetylene method for the slowest circulation time.

TABLE 7.—COMPARISON BETWEEN FLUORESCEIN AND ACETYLENE METHOD IN CIRCULATION TIMES

No.	Name	Fastest circ. time fluorescein (sec.)	Slowest circ. time acetylene (min.)	Remarks
1	Ba	7	$1\frac{1}{2}$	Exercising
2	Sa	10	2	
3	Me	12	2	
4	Scha	13	2	
5	Sto	14	$2\frac{1}{2}$	
6	Ke	18	2	
7	Re	23	3	In failure
8	He	24	3	
9	We	24	$3\frac{1}{2}$	Myxedema
10	Schar.	26	4	In failure
11	Sm	27	$3\frac{1}{2}$	In failure
12	Hi	28	$3\frac{1}{2}$	Myxedema
13	Kn	33	5	In severe failure

The shape of the curve in all our cases was practically identical, so that the average circulation time must have varied in the same proportion. In order to show how a local impairment of the backflow of blood would have influenced such a curve, blood pressure cuffs were applied to the thighs of a patient using subdiastolic pressure to keep blood artificially in those extremities. After the normal lapse of time the acetylene curve reaches its straight level (Fig. 4). This level, however, is considerably lower than the acetylene content of the inspired air, probably because blood constantly leaks out of the artificially produced blood depots. After the curve becomes straight the cuffs

were suddenly released. Within a few seconds additional acetylene was absorbed, indicating that blood previously unsaturated now entered the rapid circulation. As expected, the fluorescein circulation time did not show any variation when obtained at the moment of the release of the cuffs.
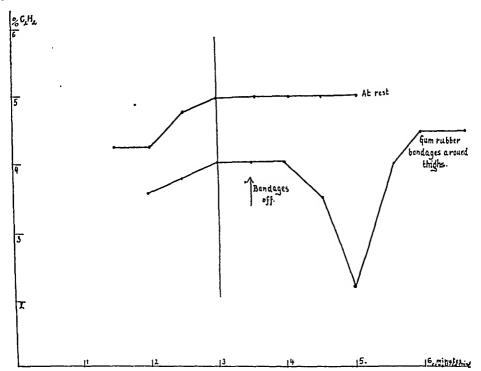
FIG. 4.—Acetylene concentration in the exhaled air of a patient who breathes a 6% acetylene-oxygen mixture. The point when the curve reaches stabilization represents the moment when all blood in rapid circulation has at least once passed the lungs. The lower curve is taken from the same patient with gum rubber bandages around the thighs. After stabilization has been reached the bandages were released. Ordinates: % acetylene. Abscissæ: minutes.

When a patient exercises while breathing the acetylene mixture, the time required for the curve to attain the straight line is very short. Using an exertion of 1200 mkg./min. the slowest circulation time became $1\frac{1}{4}$ minutes, which is approximately $2\frac{1}{2}$ times faster than normal. The fluorescein circulation time in this instance became 7 seconds in comparison to 17 seconds, the basal value for the fastest circulation time of this patient. After reaching the straight level, the expired gas mixture of the exercising patient has practically the same acetylene concentration as the inhaled gas mixture. This suggests that during work nearly all blood depots are used to provide oxygen carriers in the rapid circulation.

Summary. 1. The appearance of fluorescein in the lips under a special long-wave ultraviolet light can be used to determine the circulation time, but certain conditions must be observed in order to obtain reliable results.

2. In 212 normal adults, the values for the fluorescein circulation time ranged between 15 and 20 seconds, the majority between 15 to 17.5 seconds.

3. The average of the circulation time is longer in older patients.

4. Work accelerates the circulation time considerably and may make it $2\frac{1}{2}$ times faster than normal.

5. Fever shortens circulation time (6 cases).

6. The fluorescein method can be used to determine the velocity to different points of the body. The average time to conjunctiva, lips, rectum, foot, is 10, 15, 18 and 23 seconds, respectively. The conjunctiva is not an appropriate place to test the circulation time.

7. In congestive right heart failure 92% of the cases (123 patients) show a prolonged circulation time, while compensated cases of heart disease have normal circulation times.

8. Pure bronchial asthma, having a normal or slightly shortened circulation time, can be differentiated by the fluorescein circulation time from cardiac asthma, which has a prolonged circulation time.

9. Hyperthyroidism is associated with shortened circulation time values, which seems to provide an earlier indication of the clinical situation than the basal metabolic rate.

10. Patients with hypothyroidism have prolonged circulation times.

11. Anemia considerably shortens the circulation time when the red blood cell count goes below 3,500,000.

12. Inhalations of acetylene can be used to determine the time which elapses until all blood in rapid circulation has passed the lungs at least once ("slowest circulation time"). (a) Twenty-four normals had the slowest circulation time of $2\frac{1}{2}$ to $3\frac{1}{2}$ minutes. (b) Ten cases of thyrotoxicosis showed slowest circulation times of from $1\frac{1}{2}$ to 2 minutes while patients in cardiac failure have slowest circulation times up to 6 minutes. (c) Work shortens the slowest circulation time as much as $2\frac{1}{2}$ times the normal. (d) The comparative values found with the fluorescein method for the fastest and the acetylene method for the slowest circulation time show the same relation.

REFERENCES

1. BAUMANN, H.: Ztschr. f. klin. Med., 121, 263, 1932.
2. BERLINER, K., and LILIENFELD, A.: AM. J. MED. SCI., 203, 349, 1942.
3. BIELSCHOWSKY, P., and LANGE, K.: Deutsch. med. Wchnschr., 59, 1637, 1933.
4. BLUMGART, H. L., and YENS, O. C.: J. Clin. Invest., 4, 1, 1927.
5. BORNSTEIN, A.: Verhandl. d. deutsch. Kongr. f. inn. Med., 29, 457, 1912.
6. BOWER, J. O., and MENGLE, H. A. K.: J. Am. Med. Assn., 106, 115, 1936.
7. FISHBACK, D. B., GUTTMAN, S. A., and ABRAMSON, E. B.: AM. J. MED. SCI., 203, 535, 1942.
8. GIFFORD, H.: Arch. Ophth., 24, 122, 1940.
8a. GROLLMAN, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C Thomas, 1932.
9. HAMBURGER, C.: Ber. ü. d. Versamml. d. ophth. Gesellsch., 12, 119, 1913.
10. HERRLIN, J. O., GLASSER, T. S., and LANGE, K.: Arch. Surg., 45, 785, 1942.
11. KOCH, E.: Arch. f. klin. Med., 140, 39, 1922.
12. LANGE, K., and BOYD, L. J.: Med. Clin. North America, 26, 943, 1942.
13. LAUBER: In Kollmer and Lauber Handbch. mikrosk. Anat. d. Mensch., Haut und Sinnesorgane, II Aufl., 1936.
14. LEINOFF, H. D.: J. Am. Med. Assn., 105, 1759, 1935.
15. MÜLLER, O.: Die feinsten Blutgefässe des Menschen, Stuttgart, Enke, vol. 1, 1937.
16. PLOTZ, M.: Ann. Int. Med., 13, 151, 1939.
17. ROBB, G. P., and WEISS, S.: Am. Heart J., 8, 650, 1933.
18. STRAUSS, H.: Berl. klin. Wchnschr., 50, 2226, 1913.
19. WEISS, S., ROBB, G. P., and BLUMGART, H. L., Am. Heart J., 4, 664, 1929.
20. WOLLHEIM, E., and LANGE, K.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. Kong., 43, 134, 1931.

CONGENITAL HEART BLOCK

A Study of Two Cases in Healthy Adults

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Congenital heart block is a rare anomaly; only 80 cases were described up to 1942. It is particularly uncommon to find congenital heart block in adults in the age group presented here.

Case Reports. Case 1. The patient (Mrs. M. S.) is a 20 year old white female who has been seen at intervals for the past 4 years, during which time she has complained chiefly of easy fatigue and weakness.

Past History. The patient was born prematurely after 7 months' gestation. The delivery was normal. Her infancy was normal except for some feeding difficulties; no cyanosis was recorded at any time during infancy or childhood. At the age of 6 the patient was examined by a school physician who reported that she had a very slow pulse rate and a heart murmur. These findings were constant during her school life, but she carried on all activities and participated in all school sports without experiencing any dyspnea, palpitation, syncope or other symptoms of heart disease. She had chicken-pox and measles during childhood, but did not have diphtheria, tuberculosis or rheumatic fever.

Physical Findings. On her first visit in March, 1938, the patient was a thin, white female, height 67 inches, weight 122 pounds. Neither the skin nor the nail beds gave evidence of cyanosis. There was no clubbing of the fingers or toes. The thyroid gland was not enlarged. The apex of the heart was in the 5th interspace, 9 cm. from the mid-sternal line. At the apex, there was a soft, blowing, systolic murmur which occupied the entire systolic phase and was transmitted medially and upward toward the base. The second sound was accentuated; no thrill was palpable. The pulse was 38 and regular. The blood pressure was 100/70. The lungs were clear. The liver and spleen were not palpable. There was no edema of the extremities. There were no congenital deformities.

Laboratory Findings. The urine was negative; blood count normal; Wassermann negative; tuberculin test negative. The basal metabolism was −18%. The roentgenogram of the lungs was normal. Roentgen-ray examination of the heart showed it to be normal in size and shape (Fig. 1). Fluoroscopic examination also revealed no cardiac abnormalities in the antero-posterior, right or left oblique positions. An electrocardiogram showed complete auriculo-ventricular dissociation. There was a 2:1 block present; the auricular rate was 84, while the ventricular rate was 42 (Fig. 2). Both adrenalin (1 to 1000) and atropine sulfate ($\frac{1}{150}$ gr.) were administered separately on several occasions; neither of these drugs changed the pulse rate appreciably nor restored regular sinus rhythm.

Diagnosis. A diagnosis was made of congenital heart disease; complete heart block; and probable interventricular septal defect.

Course. During the past 4 years, the patient has been in good health except for occasional colds. She has worked as a secretary and has been married for the past year. However, she has complained constantly of easy fatigue and weakness. Her pulse has varied between 35 and 45 per minute and has been regular at all times. She has had no attacks of syncope. The basal metabolism has been repeated several times and has ranged between −18% and −8%. The patient has been given several courses of thyroid which made her feel symptomatically better, increased her ability to do things, and helped her gain some weight (15 pounds in 4 years). The thyroid medication never appreciably altered the pulse rate.

CASE 2. The patient (Mrs. C. D.) is a 31 year old white female who has been under medical observation for congenital heart disease ever since birth; yet she has been able to undergo 2 pregnancies, and lives a fairly normal life at the present time.

Past History. The patient was born at term, but was a blue baby at birth and she was considered to have congenital heart disease. At the age of seven months, she was seen by Dr. Charles Gilmore Kerley. At that time she had a loud systolic murmur at the apex and became cyanotic on exertion.* At the age of 3, she had an illness which was considered to be poliomyelitis. She wore braces on her lower legs for 2 years following this, and has enjoyed normal function of her extremities since that time. When she was 9 years old, an
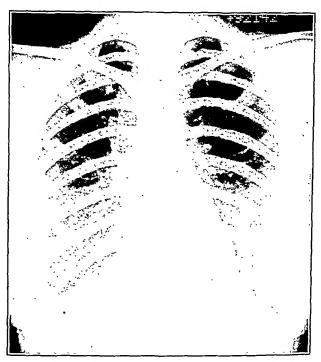
FIG. 1.—M. S. Heart size and shape are essentially normal.

electrocardiogram showed the presence of complete heart block which was felt to be truly congenital in origin. In 1924, she came under the care of Dr. Harold E. B. Pardee who felt that the history together with the electrocardiographic evidence predicated the diagnosis of congenital heart block. In 1927, she was seen by one of us and a tracing was made (Fig. 3). This showed complete auriculo-ventricular block.

Physical Findings. In 1927, the patient was a thin, white female of 17. There was no cyanosis and no clubbing of the fingers or toes. The apex impulse was in the 5th interspace, well inside the mid-clavicular line. She had a harsh, blowing, systolic murmur which was heard loudest at the 2d and 3d left intercostal spaces and was transmitted upward. The pulse rate was 35; the blood pressure was 90/60. The lungs were clear; the liver and spleen were not palpable. There was no edema of the extremities.

Laboratory Findings. The urine was negative; blood count essentially normal. The Wassermann and tuberculin tests were negative. An orthodia-

* Personal communication from Dr. Kerley.
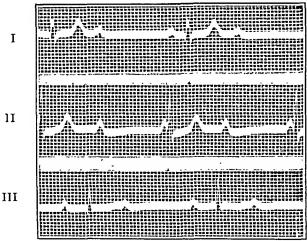
Fig. 2.—M. S. Electrocardiogram shows complete auriculo-ventricular block.
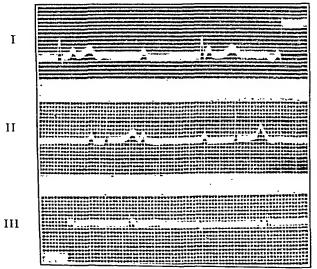
Fig. 3. C. D. Electrocardiogram taken in 1927 shows complete heart block.
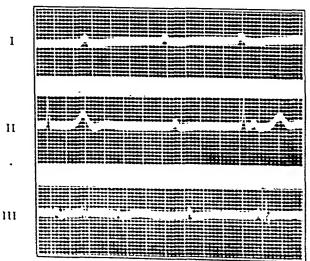
Fig. 4.—C. D. Electrocardiogram taken in 1941. This tracing is almost identical with the one taken in 1927 (Fig. 3).

graphic tracing gave a measurement of 13.5 cm. for the transverse diameter of the heart. An electrocardiogram showed complete auriculo-ventricular block. The auricular rate was 75, while the ventricular rate was 35.

Diagnosis. A diagnosis was made of congenital heart disease; complete heart block; and probable interventricular septal defect.

Course. Under Dr. Pardee's supervision, the patient has undergone two pregnancies successfully. During the last quarter of the first pregnancy (in 1935), she experienced some dyspnea. During delivery her pulse rate gradually increased and at one point was 68 per minute. This increase in rate was due to the appearance of premature beats which started about an hour before delivery. Her pulse rate dropped back to 44 15 hours after delivery. Her respiratory rate increased to 32 per minute before delivery, but decreased to 23 6 hours thereafter and did not rise again. She had a slow but uneventful convalescence. The second pregnancy came in 1938. This delivery was short and uneventful; there was no rise of pulse or respiratory rate of any significance. In December 1940, when she was under considerable strain because of illness in the family, she had several fainting spells which sounded like Stokes-Adams seizures. However, no observation was made on her during these attacks. An electrocardiogram taken by Dr. Pardee in 1941 shows that complete A–V block is still present (Fig. 4).* At the present time the patient is well and able to carry on the usual activities of taking care of her home and 2 children without discomfort of any sort.

Comment. Both these patients have lived fairly normal lives in spite of the fact that they have complete heart block of congenital origin. Mrs. C. S. is not only in an age group seldom reported with congenital block, but she has also carried two pregnancies through to term.

According to Yater,[5] heart block of congenital origin is distinguished by the following conditions: (1) An electrocardiogram which shows complete block. (2) A slow pulse that has been noticed at an early age and has continued to be present. (3) The absence of any history suggestive of an infection that might produce block; these infections are diphtheria, tuberculosis, syphilis and rheumatic fever. (4) Syncopal attacks. (5) The presence of a congenital heart lesion, usually a patent interventricular septum.

Both patients presented herewith have electrocardiographic evidence of block. Mrs. M. S. has had a slow pulse from childhood; Mrs. C. D. was considered to have congenital heart disease from birth and has had *electrocardiographic evidence of heart block since the age of 9.* Neither of the patients has a history nor laboratory findings which would indicate an infection as the cause of the block.

Mrs. M. S. has never had syncopal attacks, but Mrs. C. D. has had several fainting spells. Since the latter's pulse rate often dropped below 30 (Fig. 4) the basis for the syncope is evident. The electrocardiogram of both cases showed normal ventricular complexes. Leech[?] points out that when this occurs the block must be in the course of the main bundle of His above the bifurcation.

Both patients possess rough, low-pitched, systolic murmurs heard loudest in the 2d and 3d interspaces. Due to the character and location of these murmurs, it has been assumed that they are caused by an interventricular septal defect. According to Wallgren and Win-

blad[4] 66% of the reported cases of congenital heart block have this anomaly. Only 11 of the reported cases have come to autopsy. Six of these showed interventricular septal defects; 2 had a patent ostium primum; 3 had intact septa. These findings would seem to indicate that interruptions in the conduction system are not necessarily associated with septal defects but may be independent malformations. Septal defects are the commonest congenital cardiac anomalies (Abbott[1]) yet congenital heart block is rare. Fleming and Stevenson[2] believe that this is due to the fact that the usual septal defects are anterior to the pars membranacea while the main bundle of His lies behind it.

Complete congenital heart block is not in itself fatal. The cases presented herewith give further evidence that it is possible for a person with this anomaly to reach adult life without serious cardiac symptoms.

Summary. Two cases of congenital heart block are reported. The first case, which has been studied for 4 years, is a healthy adult who has no cardiac symptoms and no other apparent anomalies. The second case, which has been followed from birth, has had no cardiac symptoms except for some syncopal attacks. This case is of particular interest in that the patient has had two normal pregnancies without any serious cardiac disturbance.

REFERENCES

1. Abbott, M., Osler, S., and McCrae, T.: Modern Medicine, London, 4, 687, 1927.
2. Fleming, G. B., and Stevenson, M. M.: Arch. Dis. Child., 3, 221, 1928.
3. Leech, C. B.: Am. J. Dis. Child., 39, 131, 1930.
4. Wallgren, A., and Winblad, S.: Acta pædiat., 20, 175, 1937.
5. Yater, W. M.: Am. J. Dis. Child., 38, 112, 1929.

SYPHILITIC ANEURYSM OF CELIAC ARTERY

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Aneurysms of the celiac artery are rare, but somewhat less so than is true of the branches of this artery. A moderate number of reports of celiac aneurysms has appeared in the world's literature, but the descriptions are often so brief and in some instances so obviously inaccurate that the exact situation and etiology are obscure. Thirty-two of the reported cases can be accepted as true aneurysms of the celiac artery, all having been proven by autopsy. Seven of these (Archer,[1] Aronssohn,[2] Baccelli,[3] Bergeon,[9] Concato,[12] Maunsell,[31] Omodei-Zorini[32]) were probably due to syphilis. In 21 (Balme-Dugarray,[4] Bartholow,[5] Baynham,[7] Bruen,[10] Cleveland,[11] Cutler[13] [2 cases], Dowse,[14] Federici,[15] Graziadei,[19] Heitz,[20] Holmes,[21] King-Fretz,[23] Klob,[24] LeVay,[25] Lewis,[27] Lieutand,[28] Lyman,[29] McCarthy,[30] Panizza,[33] Solis-Cohen[35]) the etiology was either unknown or not stated. In 3 instances (Gorham,[18] Omodei-Zorini,[32] Sas[34]) the possibility of trauma being the

responsible factor was worthy of consideration. In the curious case described by Kolisko[25] the finding of a hog bristle in the aneurysmal wall suggests that the patient might have swallowed the bristle which had lodged in the aneurysm after passing through the wall of the intestine. At that time the bakers of Vienna used hog bristle brushes in making bread.

The first case confirmed by autopsy was described by Bergeon in 1830. The patient had general paresis and the aneurysm of the celiac artery was presumably syphilitic.

In 1862, Concato[12] described a typical aneurysm of the celiac artery which was diagnosed in life. The patient was a 38 year old male who had syphilis, epigastric pain, fever and a pulsating abdominal tumor mass. Autopsy revealed a ruptured saccular aneurysm of the celiac artery.

The last recorded case (1941, LeVay) was that of a 58 year old white female who had signs and symptoms of acute cholecystitis— vague gastro-intestinal symptoms for some 6 months, then sudden severe epigastric pain radiating to the right shoulder, nausea, slight icterus and fever. There were signs of localized peritonitis and a palpable mass in the right upper quadrant. The patient died suddenly 6 days later. Autopsy revealed an aneurysm of the celiac artery which had ruptured into the lesser peritoneal cavity. Death was due to pulmonary embolism arising from a thrombus in the compressed inferior vena cava. The pain in the shoulder and icterus were thought to be due to pressure on the diaphragm and bile ducts respectively. There was no evidence of syphilis and there was very little arteriosclerosis. Other cases are indicated in the bibliography at the end of this paper.

Three cases (Battaglia,[6] Smith,[35] Soós[37]) of false or spurious aneurysm of the celiac artery, tuberculous in origin, have been reported. In all 3, caseous tuberculosis of the regional lymph nodes evidently had extended to the celiac artery, resulting in tuberculous arteritis and aneurysm formation.

A fourth case of spurious aneurysm of the celiac artery was reported by Irvine.[22] The patient had nephrolithiasis, pyelonephritis and extensive suppuration of the retroperitoneal tissues. The extension of the acute inflammatory process to the celiac artery resulted in destruction of its wall and localized dilatation.

In the case to be reported, the aneurysm was due to syphilis. It is the only instance of aneurysm of the celiac artery in 8070 autopsies performed at the Institute of Pathology of Western Reserve University and University Hospitals.

Case Report. A negro, aged 44, was first admitted to the hospital December 29, 1941. His chief complaint was constant epigastric pain which radiated laterally along both costal margins. He had had similar epigastric pain, intermittent in character, for over 3 years.

Physical Examination. Temperature 37.4° C., pulse 96, respirations 22, blood pressure 160/114. The heart was slightly enlarged to the left and there were systolic and diastolic apical murmurs. In the left upper quadrant of the abdomen there was a pulsating, firm, tender, fixed mass, measuring about

6 cm. in diameter.   Roentgen ray and fluoroscopic examination revealed an enlarged left ventricle, slight dilatation of the ascending aorta, and calcareous deposits in the abdominal mass.   The blood Kline exclusion test was negative.

At this time the most probable diagnosis was thought to be syphilitic aortitis with aortic insufficiency and aneurysm of abdominal aorta.   He was discharged
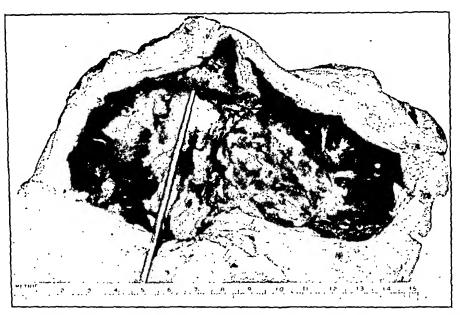
Fig. 1.—Photograph of the aneurysm, including a portion of the aorta. The probe lies in the lumen of the aneurysm and continues in the lumen of the celiac artery.
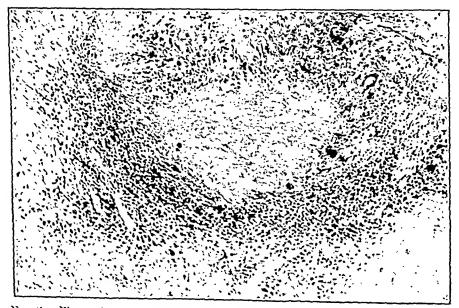
Fig. 2.—Photomicrograph of the aorta showing miliary gumma in media.   × 165.

after 5 days and subsequently visited the dispensary regularly. The epigastric pain persisted but was sufficiently relieved with analgesics to enable him to work as a garbage collector for 3½ months. In the latter part of April, 1942, he noticed increasing weakness, generalized muscular soreness, shortness of breath on exertion, and at night frequently had chills, fever and night sweats.

Two weeks before readmission to the hospital he first noticed swelling of the ankles and 10 days later vomited some clotted blood. From this time on his stools are said to have contained bright red blood.

He was readmitted on May 30, 1942.

Physical Examination. Temperature 40.1° C., pulse 96, respirations 20, blood pressure 140/70. There was slight pallor and slight generalized icterus. The pupils did not react to light. There was no noteworthy change in the heart. The pulsating tender abdominal mass was still present, measuring about 7 cm. in its greatest diameter. The liver extended 2 cm. below the costal margin in the right midclavicular line and was slightly tender. There was marked cutaneous hyperesthesia over the abdominal mass.

Laboratory Reports (day of admission). Urine: sp. gr. 1.015; contained bile pigment and a few white blood cells, no casts, albumin and sugar negative. Blood: 24,000 WBC (85% neutrophils, 12% lymphocytes, 3% monocytes), 2.5 mill. RBC, 45% Hgb. (Sahli); negative Kline exclusion test; icterus index 19.

Hospital Course. The patient continued to pass blood by rectum and his hemoglobin gradually fell, in spite of 3 transfusions of whole blood totaling 1600 cc., to 28% on his 16th hospital day. The icterus index rose to 30 by his 17th hospital day. He had a continued spiking temperature with a maximum of 39° to 40° C. in the late evening. At times he was mentally confused and irrational. On his 18th hospital day he vomited a large amount of bright red blood, soon became comatose and died shortly thereafter.

Autopsy (No. 7804 by Dr. W. B. Chamberlin, Jr.). The most significant observation was a syphilitic saccular aneurysm of the celiac artery measuring 15 x 7 x 4 cm. All of the branches of this vessel were normal. The aneurysm was approximately in the midline. It had compressed and destroyed a large portion of the head of the pancreas. There was a direct communication between the main pancreatic duct and aneurysmal sac. Clotted blood was present in the distal 3 cm. of the pancreatic duct and projected from the ampulla of Vater. There was also considerable clotted blood throughout the gastro-intestinal tract. In its proximal two-thirds, the pancreatic duct was distinctly dilated and there was moderate fibrosis of the entire pancreas. The aneurysm had also displaced, compressed and partially obstructed the second portion of the duodenum and common bile duct. The extrahepatic and intrahepatic bile ducts were markedly dilated and there was ascending acute cholangitis with multiple small abscesses in the liver. Generalized icterus of moderate degree was present with an associated cholemic nephrosis. Indisputable gross and microscopic stigmata of syphilis were present in the thoracic and abdominal portions of the aorta. There was also syphilitic valvulitis and slight insufficiency of the aortic valve. No spirochetes could be found in the aorta or aneurysmal wall, but a miliary gumma was demonstrated in the aortic arch. The inner surface of the aneurysm showed numerous large projecting pale bluish-gray, translucent, hyalinized intimal plaques. There were few atheromatous masses and there was little calcification. Within and between the projecting intimal plaques there was retraction of intima producing stellate and parallel depressed lines. These gross findings are typical of syphilitic arteritis.

Comment. Both clinically and pathologically the case reported is unusual. Generalized icterus and bleeding from the gastro-intestinal tract are uncommon clinical manifestations of abdominal aneurysms. Jaundice is particularly rare. The celiac artery and one of its branches, the hepatic artery, are in close proximity to the extrahepatic bile ducts, a relationship which makes compression and obstruction of the bile ducts by aneurysm of these vessels a likelihood, with consequent generalized icterus. It is worthy of note that in such cases the signs and symptoms may simulate acute cholecystitis or primary hepatic disease.

Hemorrhage into the gastro-intestinal tract in patients with aneurysms of large vessels is usually due to erosion of esophagus, stomach or intestine and rupture of the aneurysmal sac into the lumen of one of these viscera.   In this case there was erosion of and rupture into the main pancreatic duct with hemorrhage into the gastro-intestinal tract by way of the ampulla of Vater.

The rarity of the situation of the aneurysm in this case is indicated by the fact that only 32 acceptable cases of aneurysm of the celiac artery are found in the literature.   In all but 2 cases, death resulted from rupture of the aneurysm and hemorrhage into the peritoneal cavity or retroperitoneal tissues.   In 3 cases syphilitic arteritis was established as the cause.   In most instances the etiology was unknown or not stated.   The majority of the cases, however, were reported before 1895, when Döhle first established the relationship between mesaortitis and syphilis.   It is, therefore, probable that many considered to be of unknown cause were syphilitic.   False aneurysms of this artery occasionally result from tuberculosis, acute suppurative inflammation and possibly trauma.

Miliary gummas are not commonly demonstrated in chronic syphilitic aortitis.   Gordon, Parker and Weiss[17] found microscopic gummas in 8 of 360 cases, an incidence of 2.2%.

Summary.   Review of the literature shows that aneurysm of the celiac artery is rare.   The case reported is one of saccular syphilitic aneurysm of the celiac artery complicated by bleeding into the intestinal canal by way of the pancreatic duct.   The signs and symptoms simulated acute cholecystitis.

REFERENCES

1. Archer, R. S.:   Irish Hosp. Gaz., Dublin, **3**, 4, 1875.
2. Aronssohn: Gaz. méd. de Strasb., M. **12**, 258, 1866.
3. Baccelli, G.:   Policlini., **14**, 93, 1907.
4. Balme-Dugarray, M.:   Bull. Soc. anat. de Paris, **3**, 6, 1836 (3s, 2).
5. Bartholow, R.:   West. J. Med., **3**, 160, 1868.
6. Battaglia, M.:   Ann. di med. nav. Roma, **10**, Pt. I, 606, 1904 (1 pl.).
7. Baynham, J. M.:   Midland Med. and Surg. Rep., **3**, 125, 1831–2.
8. Bérard, P. H.:   Dict. de méd., **8**, 165, 2. ed., Paris, 1834.
9. Bergeon: Rev. méd. franc. et etrang., Paris, **3**, 219, 1830.
10. Bruen, E. T.:   Trans. Path. Soc. Phila., **10**, 99, 1882.
11. Cleveland, J. L.:   Cincinnati Lancet and Clinic, **12**, 259, 1884.
12. Concato, L.:   Ann. univ. di med., Milano, **181**, 343, 1862.
13. Cutler, E. G.:   (a) Med. and Surg. Rep. Boston City Hosp., **3**, 376, 1882; (b) Ibid., **3**, 377, 1882.
14. Dowse, T. S.:   Med. Times and Gaz., London, **1**, 281, 1877.
15. Federici, C.:   Rev. clin. di Bologna, **1**, 577, 1881.
16. Friedenwald, J., and Tannenbaum, K. H.:   Am. J. Med. Sci., **165**, 11, 1923.
17. Gordon, W. H., Parker, F., Jr., and Weiss, S.:   Arch. Int. Med., **70**, 396, 1942.
18. Gorham, R. V.:   Prov. Med. and Surg. J., London, **13–14**, 371, 1850.
19. Graziadei, B.:   Clin. med. ital., **40**, 720, 1901.
20. Heitz, P. A.:   Trans. Minnesota Med. Soc., p. 91, 1887.
21. Holmes, T.:   Trans. Path. Soc. London, **9**, 172, 1857–8.
22. Irvine, J. P.:   Trans. Path. Soc. London, **29**, 85, 1878.
23. King-Fretz, H. E.:   J. Roy. Nav. Med. Ser., London, **3**, 342, 1917.
24. Klob, J.:   Aneurysma dissecans arteriae coeliacae. Ber. d. k. k. Krankenanst. Rudolph-Stiftung in Wien (1865), p. 186, 1866.
25. Kolisko, A.:   Wien. klin. Wchnschr., **5**, 321, 1892.
26. LeVay, A. D.:   Brit. J. Surg., **28**, 502, 1911.
27. Lewis, T. C.:   Lancet, **1**, 495, 1842.

28. LIEUTAUD (cited by BERARD, P. H.): Dict. de méd., 2 ed., Paris, 8, 165, 1834.
29. LYMAN, G. H.: Extr. Rec. Boston Soc. Med. Impr., 7, 142, 1879.
30. McCARTHY, D. J.: Trans. Path. Soc. Phila., 18, 216, 1898.
31. MAUNSELL, C. B.: Brit. Med. J., 1, 272, 1899.
32. OMODEI-ZORINI, A.: Arch. ital. di chir., 12, 443, 1925.
33. PANIZZA, M.: Gior. internaz. d. sc. med. Napoli, n.s., 1, 241, 1879.
34. SAS, J. J.: Nederl. Lancet, Utrecht., 2, 645, 1839–40.
35. SMITH, R. P.: Newcastle Med. J., 7, 133, 1927.
36. SOLIS-COHEN, S.: Trans. Path. Soc. Phila., 18, 165, 1898.
37. SOÓS, J.: Gyógyászat, 68, 142, 1929.

LOCALIZED AGNOTOGENIC (OF UNKNOWN ORIGIN) XANTHO-MATOSIS OF SPLEEN WITH SPLENOMEGALY AND ANEMIA

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THE formulation of a rational basis of classification for the lipoidoses has been made possible in recent years by the chemical isolation of the specific substances accumulated and deposited during the course of the disease. The chemical structure of these substances, their interrelationship and pathologic significance are indicated in Figure 1.

Thus, the chemical nature of the accumulated lipoid determines the classification. It is recognized, however, that other related lipoids may also be present in quantities above normal.

Further subdivisions may be made and are desirable according to the organ or organs involved and the clinical course.

At present, the following clinical forms are recognized:*

A. Cerebroside lipoidosis: Morbus Gaucher: (a) infantile form; (b) adult form.

B. Phosphatide lipoidosis: (a) Niemann-Pick's disease; (b) amaurotic familial idiocy.

C. Xanthomatosis or cholesterol lipoidosis: I. Idiopathic: (a) acute: Letterer-Siwe's disease; (b) chronic: (1) Hand-Schueller-Christian's syndrome; (2) cutaneous: disseminate and tuberous form; (3) cerebral; (4) pulmonary; (5) cardiovascular; (6) hepatic; (7) osseous; (8) splenic.
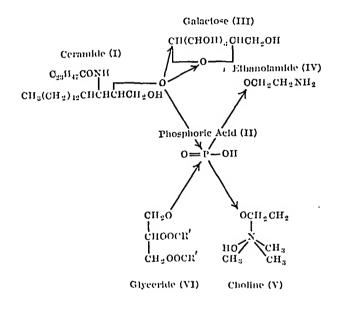
II. Secondary: (1) diabetic; (2) icteric; (3) nephritic; (4) dietary; (5) experimental.

In most instances, the visceral xanthomatoses are combined with one or the other type of cutaneous lesion. According to Thannhauser and Magendantz,[27b] a definite correlation exists between the type of cutaneous lesion and the localization in the viscera. Thus, it would be possible to predict from the character of the xanthomatous skin lesion, the organ involved in a similar process.

* Comprehensive discussions of the lipoidoses may be found in the articles and monographs of Buerger,[4] Epstein,[8] Jaffé,[12] Pick,[18] Rowland,[21] Thannhauser.[27]

The various forms of essentially visceral xanthomatosis form a residual group.[18]   Only the syndrome of Hand-Schueller-Christian has received consideration comparable to that given to Gaucher's and Niemann-Pick's disease.   The other types are not well known, particularly as there are only few chemical data available.[9,13,25]   Xanthomatosis envolving primarily the brain has been described by Bogaert and Scherer[3] together with Epstein and Lorenz[8a].   Primary palmonary xanthomatosis has been discussed by Noethen.[17]   Recently, Mueller,[16] and Bloom, Kaufman and Stevens[1] published several cases of familial xanthomatosis of the skin and emphasized the rôle of familial xanthomatosis in hereditary heart disease.   Cases with xantho-

$$I + III = Kerasin = Gaucher's$$
$$I + II + V = Sphingomyelin = Niemann-Pick's$$
$$VI + II + V = Lecithin$$
$$VI + II + IV = Cephalin \quad\Big\rangle Xanthomatosis$$

Fig. 1.—Chemical interrelationship of the substances deposited in the principal clinical forms of lipoidosis.

matosis of the biliary system have been investigated by Buerger,[4] Thannhauser,[25a,b] and others.   Xanthomatosis of the bones has been described by Chester.[5]

All these localized forms of xanthomatosis encroach upon the function of the organ involved.   We have had occasion to study a case of primary xanthomatosis of the spleen with splenomegaly and anemia as the main clinical symptoms.   This anemia disappeared after splenectomy.   We have not found a similar case in the literature.

Case Report.   Nancy C., white, aged 6, of English-Scottish stock, was born, at term, from healthy parents.   She weighed 8½ pounds.   She had measles but none of the other infectious diseases of childhood.   She used to have frequent attacks of tonsillitis which stopped after a tonsillectomy was

performed when she was 5 years old. However, since that time, she was not well, tired easily, became pale and developed *café au lait* colored spots and blotches on the trunk, face and thighs. She had never been very strong and her appetite was always poor. When she was 1 year old, she had an attack of vomiting, fever and epigastric pain which lasted several days. As an infant, she had fainting spells after "holding her breath." Since then, and up to the present time, she used to wake up in the middle of the night feeling faint and being confused, sometimes vomit and wet her bed. Such episodes occurred at intervals of 4 to 6 weeks. Similar attacks occurred occasionally after exertion. No such attack was ever witnessed by a physician. Her sleep was always very light. Her mental development was normal and she did very well in school.

Her local physician found her anemic (no data available) and gave her appropriate doses of iron and liver extract without any improvement in the anemia which was said to have been moderate. She then was seen in consultation by Dr. M. M. Fliess* who noticed a marked enlargement of the spleen and found her red count between 3.5 and 4 M/c.mm. The medical treatment was continued for a while but without result. She was then referred to the Chesapeake & Ohio Hospital, Clifton Forge, Va., for further study.

On admission (3–12–41), she did not appear acutely ill. She was a delicate, well-developed and fairly well-nourished child. Her skin was of fine texture, moist, pale, with irregular *café au lait* blotches on both sides of the thorax, on one cheek, on both thighs and arms. There was no thickening of the skin and no induration. The spleen was palpable 3 fingers below the ribs. It seemed smooth and firm. No lymph nodes were palpable. The mucous membranes were pale. Otherwise the physical examination was entirely negative. Temperature, pulse and respiration were normal.

Laboratory Tests. Urine: no abnormal constituents. Blood: red cells, 3,145,000; hemoglobin, 64% (Hellige); color index, 0.94; volume index, 1.1; slight anisocytosis; no sickle cells, no spherocytes, no nucleated red cells; white cells, 5100 (segmented neutrophils 50%, stabs 5%, monocytes 3%, eosinophils 2%, lymphocytes 40%); platelets, 180,000; bone marrow: normal composition, no abnormal cells; bleeding time, 4 minutes; coagulation time, $4\frac{1}{2}$ minutes; fragility of red cells: partial hemolysis at 0.44% NaCl, complete hemolysis at 0.34% NaCl; icterus index, 4.6; bilirubin, less than 2.5 mg. per 100 cc; blood cholesterol, 125 mg. per 100 cc; blood urea, not determined; Exton Rose glucose tolerance test (at a later date—6-17-42): 124.2, 99, 82 mg. per 100 cc; blood pressure, 100 systolic, 65 diastolic.

Roentgenographic Studies. The pituitary fossa was normal in size and regular in outline. No lesions of the bony skull, the ribs and the extremities were noted. The lung fields were clear.

In view of the splenic enlargement and leukopenic anemia which had proved absolutely refractory, it was decided to perform an exploratory laparotomy with possible removal of the spleen. The possibility of a lipoidosis was considered but the absence of abnormal cells in the bone marrow and negative roentgenologic findings seemed to speak against this diagnosis.

Operation: The spleen was removed in the usual manner after separating some adhesions. Inspection of the abdominal organs, especially the liver, showed none of them unusual. The postoperative course was uneventful. Four days after operation the blood count was: red cells, 4,550,000; white cells, 16,700 (segmented neutrophils 71%, stabs 13%, monocytes 4%, eosinophils 0%, lymphocytes 12%); platelets, 273,000.

She was discharged 10 days after operation. Unfortunately, no close follow-up was possible. She was seen, however, once again, 14 months later. She had gained weight and grown normally. The brownish areas on her skin were still present but to a lesser degree. She still had the occasional attacks as described above. Otherwise she seemed to do well. Her blood count was: red cells, 4,440,000; hemoglobin, 96% (Hellige); color index, 1.05; white cells, 13,500 (segmented neutrophils 27%, stabs 3%, monocytes 4%, eosinophils 2%,

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* Dr. M. M. Fliess, Clifton Forge, Va., furnished the clinical data.

lymphocytes 64%); platelets, 501,000.   Her urine was normal.   The blood cholesterol was 130 mg. per 100 cc.

On June 22, 1943, the patient seemed well and has made adequate progress physically and mentally.   There were a number of small firm lymph nodes palpable in the neck, in the axillæ and in the groin.   They were not tender. I suppose they formed after removal of the spleen.   A Roentgen ray of the skull was normal.   The urine showed no abnormal findings.   Hemoglobin was 89.1% (Hellige).   Red cells, 4.43 million/c.mm.   White cells, 10,050 (69%
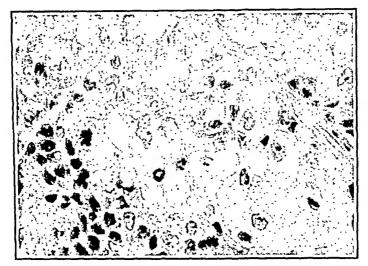
Fig. 2.—Foam cells in splenic pulp.   Stain: H. and E.   × 670.
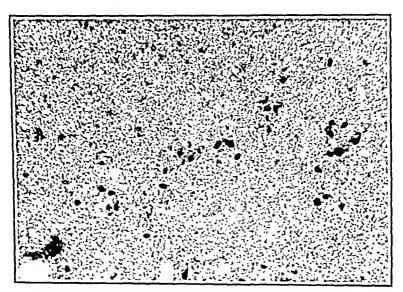
Fig. 3.—Sudanophil matter in droplet form (black in photograph).   × 80.

lymphocytes, 1% monocyte, 2% neutrophil stabs, 34% neutrophils segmented and 1% eosinophil).   The platelets were 886,000.   The hematocrit was 41. Bleeding time, 4 minutes; coagulation time, 4½ minutes.   Urea nitrogen, 10 mg. per 100 cc.   Blood calcium, 10.4 mg. per 100 cc.   Blood phosphorus, 4.5 mg. per 100 cc.   Cholesterol, 220 mg. per 100 cc.   Glucose tolerance test, 5 hours: 105, 116, 98, 74, 90, 86 mg. per 100 cc.
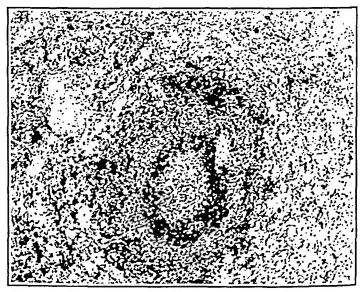
The value for cholesterol which is now high normal contrary to the low normal on previous occasions is noteworthy.

DESCRIPTION OF THE SPLEEN.   The spleen was enlarged to about 3 times its normal size.   It weighed 190 gm. and was firm.   The margins were rounded. The capsule was thin except for a few fibrous adhesions.   The vessels were normal.   The cut section was dry, dull brick red with numerous grayish miliary nodules.   Sections were stained with hematoxylin-eosin, trichrome (Foot), elastica, Sudan 4, and impregnated with silver (Foot).

Microscopic Findings.   The follicles were placed far apart due to the marked hyperplasia of the pulp.   The reticulum cells of the pulp were large.   In paraffin sections, their protoplasm was clear and foamy (Fig. 2).   The nuclei were small, dark staining and located centrally or somewhat to the periphery of the cell.   With Sudan 4, the protoplasm appeared to contain orange red droplets or fine gold brown dusty granules; frequently it was Sudan-negative (Fig. 3).   The foam cells formed heaps and strands which filled the major part of the pulp.   They were less numerous around the follicles (Fig. 4). The sinuses were compressed and almost bloodless.   Their endothelium was flat and did not contain lipoid.   In the perifollicular areas, where the lipoid-containing cells were less numerous, the sinuses were congested.   Fat was also found in the reticulum cells of the germinal centers, in perivascular histiocytes

FIG. 1.—The xanthomatous process is less marked around the follicles.   The clear zones are areas filled with foam cells.   × 108.

of the Malpighian arteries and of the trabecular vessels.   There was no inflammatory reaction.   There was no fibrosis.   No giant cells were seen.*

CHEMICAL ANALYSIS OF THE SPLEEN.   The spleen after 2 days in Kaiserling Nr. 1, was washed carefully and placed in 10% formalin.   The quantitative analysis was started a few days later.

* In this connection, we have recently had a case (Univ. of Penna. Hosp., Aut. '42-1280) of splenic lipoidosis which would probably be allocated as "secondary" in the classification below.   The patient, a 19 year old colored girl with a patent foramen ovale and mild pulmonary stenosis, developed subacute glomerulonephritis with the nephrotic syndrome and lost serum proteins until her A,G ratio was 1.2/1.7 gm.   She had a persistent hypercholesterolemia reaching 780 mg. per 100 cc.; Hb, 6.6 gm.; and normal W.B.C. counts.   At autopsy, her spleen (weight 550 gm.) was smooth, homogeneous, dull pink, flabby with bulging cut surface.   Histologic examination revealed numerous, often coalescent collections of large cells 40 to 120 micra in diameter, with

The lipoids were extracted with alcohol and ether (Bloor[2]) and isolated in petroleum ether. The phosphatides were precipitated from the petroleum ether with acetone and magnesium chloride. The lecithin and cephalin were then dissolved in ether. The lecithin was determined from its cholin content by the method of Roman[19] as modified by Kirk.[15] The diaminophosphatide was then estimated by the method of Thannhauser and Setz[27b] by precipitation with Reinecke acid. Cephalin was estimated by difference. The cerebrosides, which were present only in traces, were determined by the method of Kimmelstiel[14] as modified by Kirk.[16]

The values are expressed in mg. per 100 gm. of dry weight.

For comparison, the values of splenic lipoids in other types of lipoidosis are also tabulated:

	Dreyfuss Fishberg	Normal	Niemann-Pick	Gaucher	Tay-Sachs
Total cholesterol	6.36	0.6– 2.3	6.73	2.72	2.67
Free cholesterol	3.12	0.5– 1.1	6.70	0.52	1.00
Ester cholesterol	2.20	0.2– 1.2	0.03	2.20	1.67
Total phospholipids	18.30	5.5–11.0	42.50	9.39	6.58
Lecithin	10.24	3.1– 4.0	...	7.34	4.44
Cephalin	7.11	1.6– 4.0	...	1.50	1.23
Fatty acids	7.83	7– 9	..	6.10	7.25
Sphingomyelin	0.95	0.7– 1.0	32.70	0.55	0.91
Cerebrosides	traces	traces	...	6.65	

Comment. The outstanding feature of this case was a splenic enlargement caused by accumulation of lipoid substances in the reticulum cells of the spleen. As established by quantitative chemical analysis, the increase of lipoids was mainly in the monaminophospholipids: lecithin and cephalin. The total cholesterol was also increased from 3 to 10 times normal. The ratios between total cholesterol, ester cholesterol and free cholesterol were not markedly changed. The phospholipids were increased due to the high values of lecithin and cephalin. Sphingomyelin was present in normal amounts and thus the possibility of Niemann-Pick's disease could be discarded. The cerebrosides were found to be present only in traces and therefore Gaucher's disease was also ruled out. Accumulation of cholesterol and monoaminophospholipids, on the other hand, is characteristic for xanthomatosis, essential or secondary. The total cholesterol of the blood was low normal. The significance of this fact will be discussed later.

The chemical results fit with the histologic findings. The appearance of the protoplasm was definitely not that of the Gaucher cell. A large proportion of the lipoid-containing cells was Sudan-positive, with variation of degree. No special staining methods for lipoids were applied because it was felt that they were not very reliable. There was no double refraction, a fact for which we have no explanation. The fatty substances were present only in the reticulum cells, prevalently in the pulp but also in the Malpighian follicles and in

1 to 5 nuclei and pale pink, staining, somewhat vacuolated or rarefied cytoplasm, containing no sudanophilic nor anisotropic material. These cells were all in the pulp and extrafollicular. Elsewhere this change was found only in a few lymph nodes. The renal tubules had moderate amounts of sudanophilic material and small amounts of anisotropic substance, and the hepatic cells contained finely divided, evenly distributed droplets which stained partially with Sudan IV. We have tentatively classified this case as xanthomatosis of the spleen and lymph nodes, associated with hypercholesterolemia.—EDITOR.

perivascular histiocytes. The endothelium of the sinuses did not participate at all in the process. This fact has previously been emphasized by Pick.[18]   Fat is normally present in the spleen in small amount, mainly in the reticulum cells of the follicles. It may be considerably increased experimentally by oral or intravenous introduction of cholesterol or sphingomyelin.[19]

Lipoid-containing cells have been found in the spleen in cases of severe diabetes and in cases with diabetic lipemia. Usually, this does not cause splenic enlargement. In a small number of cases, however, a splenic tumor was present. Schultze[24] was the first to describe lipoid cell hyperplasia of the spleen in diabetes. A number of other reports followed. A certain distinction has been made between the splenic xanthomatosis associated with diabetic xanthelasma and that of diabetic lipemia. It has been claimed that in the latter, because of its more acute course, the character of the intracellular lipoids is more variable than in the former and the picture more marked. Except for the chemical analyses carried out in the cases of Fahr and Stamm[9] and Siegmund,[25] the interpretation of these cases is based solely on histochemic reactions. It seems probable that the underlying mechanism is the same in all of them and the variations do not warrant a separation into two groups.

Xanthomatosis of the spleen in non-diabetic patients has been reported by Dyke[7] and Wille-Baumkauff.[31]   Dyke found the characteristic splenic lesions in a patient with cirrhosis of the liver, pancreatitis and a hypercholesteremia of 1250 mg. per 100 cc. Wille-Baumkauff described them in 2 patients, 1 of which died of common duct obstruction, the other, at the age of 72, of generalized arteriosclerosis and renal arteriolosclerosis.

In all 3 cases, hypercholesteremia was present or highly probable. The values for total blood cholesterol in the present case were low normal. Both normal and high blood cholesterol have been observed in essential xanthomatosis. This discrepancy is important for the interpretation of the nature of the process which terminates with the accumulation of the various lipoids or lipoid mixtures in certain organs or cell systems. Some authors maintain that there is a primary disturbance of the lipoid metabolism and that the accumulating abnormal products are passively stored, preferably in cells to which they have a special affinity.[18,21]   On the other hand, it has been claimed that the lipoidoses are diseases of the reticulo-endothelial system and that the accumulation of the lipoid substances is secondary;[24,29] also that lipoid storage may be secondary to protein disturbance of renal disease. Between these points of view, various different interpretations have been brought forth: abnormal ratio between total and free cholesterol,[2] deficiency of lipolytic enzymes,[25] precipitation due to non-optimal dispersion,[30] intracellular disorder of the reticulum cells but not confined to the reticulo-endothelial system.[27]

Since our knowledge of lipoid metabolism is very incomplete, no general agreement can be expected. The present case may throw some light on a few pertinent questions.

1. There was no evidence of a general disturbance of the lipoid

metabolism. The discoloration of the skin was not that usually seen in xanthomatosis but resembled rather that of Gaucher's disease.

2. No diabetes was present. On the contrary, the blood sugar dropped, during an Exton Rose glucose tolerance test, from a fasting level of 124.2 to 82. We realize that a single curve of this type has but limited significance. However, Buerger[4] has collected a number of cases of xanthomatosis which all had low blood sugar values (down to 40 mg. per 100 cc.). These observations are in contrast to the general opinion that the sugar tolerance in xanthomatosis is usually decreased. Whether the attacks of sweating, weakness and mental disturbance, from which our patient suffered, are to be regarded as hypoglycemic episodes or whether they are epileptiform seizures, we are not able to say. It seems more likely, however, that they represent mild hypoglycemic states. At any rate, there was a disturbance of the carbohydrate metabolism which may be connected with the xanthomatous process.

3. The xanthomatosis apparently was limited to the spleen. The liver seemed normal. The pancreas was not examined at the operation. We wish to emphasize again that the endothelial cells did not participate in the changes. It seems unlikely, then, that the lesion was a general one of the reticulo-endothelial system.

4. The anemia, which was the main clinical symptom, was never very severe. It was normocytic, leukopenic, with no evidence of hemolysis. There was no hemosiderosis. The anemia improved after splenectomy and the blood count has been almost normal over a considerable period of time, except for the now present lymphocytosis —a not infrequent sequel of splenectomy in general. By what mechanism the anemia was produced, we are not able to say. The marked improvement after splenectomy certainly suggests that the pathologic changes in the spleen were responsible, perhaps by disturbing the spleen's regulatory influence on blood formation.

5. The general condition of the child also improved after splenectomy, and has remained good for over 2 years. This is additional evidence that the xanthomatosis of the spleen is here a local disorder rather than an expression of a general metabolic disturbance.

The most satisfactory interpretation of the present case seems to be that a local intracellular disorder, perhaps due to an intracellular disturbance of the lipolytic enzymes, has caused the accumulation of lipoids in the reticulum cells of the spleen. Otherwise, no such improvement as seen in the present case after splenectomy, could be explained. The possibility of an associated xanthomatosis of the pancreas may—in a speculative way—be considered in connection with the increased sugar tolerance of the patient and the probably hypoglycemic attacks.

Summary. A case of primary xanthomatosis of the spleen associated with splenomegaly (due to foam cells) and anemia in a non-diabetic child is described. The results of histologic and quantitative chemical analysis of the spleen are reported and discussed. The lipoids chiefly increased were lecithin, cephalin and total cholesterol, thus ruling out Gaucher's and Niemann-Pick's disease.

It is thought that the process represents a local intracellular disorder, perhaps due to faulty action of the lipolytic enzymes. Splenectomy was beneficial.

REFERENCES

1. Bloom, D., Kaufman, S. R., and Stevens, R. A.:   Arch. Dermat. and Syph., 45, 1, 1940.
2. Bloor, W. R.:   J. Biol. Chem., 82, 275, 1929.
3. Bogaert, L., and Scherer, H. J.:   Une forme cerebrale de la cholesterinose generalisee, Paris, Masson et Cie, 1937.
4. Buerger, M.:   Neue deutsch. Klin., 12, 583, 1934.
5. Chester, W.:   Virchows Arch., 279, 561, 1930.
6. Davison, C., and Jacobson, S. A.:   Am. J. Dis. Child., 52, 345, 1936.
7. Dyke, S. C.:   J. Path. and Bact., 31, 173, 1928.
8. Epstein, E.:   Virchows Arch., 306, 53, 1940.
8a. Epstein, E., and Lorenz, K.:   Ztschr. f. physiol. Chem., 192, 145, 1930.
8b. Epstein, E., and Lorenz, K.:   Klin. Wchnschr., 16, 1320, 1937.
9. Fahr, T., and Stamm, G.:   Monatschr. f. Kinderh., 2, 169, 1928.
10. Ferraro, A., and Jarvis, G. A.:   Arch. Pathol., 30, 731, 1940.
11. Freund, P., Grossman, L., and Dragutsky, D.:   Am. J. Dis. Child., 62, 776, 1941.
12. Jaffè, R.:   in H. Downey, Handbook of Hematology, New York, Paul B. Hoeber, 2 (sect. 15), 977, 1938.
13. Kleinmann, H.:   Virchows Arch., 282, 613, 1931.
14. Kimmelstiel, P.:   Biochem. Ztschr., 212, 359, 1929.
15. Kirk, E.:   J. Biol. Chem., 123, 613, 1938.
16. Mueller, C.:   Arch. Int. Med., 64, 675, 1939.
17. Noethen: Frankf. Ztschr. f. Path., 23, 471, 1920.
18. Pick, L.:   Am. J. Med. Sci., 185, 453, 601, 1933.
19. Roman, W.:   Biochem. Ztschr., 219, 218, 1930.
20. Rothstein, J. L., and Welt, Sara: Am. J. Dis. Child., 62, 801, 1941.
21. Rowland, R. S.:   in Brenneman, Practice of Pediatrics, 3, Chap. 23, 15, 1942.
22. Schaff, F., and Werner, H. J.:   Arch. f. Dermat. and Syph., 162, 217, 1930.
23. Schulz, A., Wermbter, F., and Puhl, H.:   Virchows Arch., 252, 519, 1924.
24. Schultze, W. H.:   Verhandl. d. deutsch. path. Gesellsch., 1912.
25. Siegmund, H.:   Verhandl. d. deutsch. path. Gesellsch., 1921.
26. Sobotka, H., Glick, D., and Tuchman, L.:   Biochem. J., 27, 2031, 1933.
27. Thannhauser, S. J.:   Lipidoses: Diseases of the Cellular Lipoid Metabolism. New York, Oxford University Press, 1940.
27a. Thannhauser, S. J., and Magendantz, H.:   Ann. Int. Med., 11, 1662, 1938.
27b. Thannhauser, S. J., and Setz, P.:   J. Biol. Chem., 116, 533, 1936.
28. Turner, A. L., Davidsohn, J., and White, A. C.:   Edinburgh Med. J., 32, 153, 1925.
29. Wallgren, A.:   Am. J. Dis. Child., 60, 471, 1940.
30. Wile, N., Echstein, H., and Curtis, A.:   Arch. Dermat. and Syph., 19, 35, 1929.
31. Wille-Baumkauff, H.:   Frankf. Ztschr. f. Path., 41, 14, 1931.

CLINICAL OBSERVATIONS ON THE EFFECT OF 3,3'–METHYL-ENEBIS (4–HYDROXYCOUMARIN)*

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During the last few years, the clinical use[1,5,6,7] of anticoagulants has greatly increased due in large part to the preparation of a non-

toxic heparin and to the excellent clinical and laboratory studies of intravascular thrombosis and embolism.*

Widespread use of heparin in the therapy of these conditions has been limited by great expense and difficulty of administration of the drug; it must be given intravenously either in a continuous infusion or by injections 3 or 4 times daily.†

Studies on the pathogenesis of hemorrhagic sweet clover disease in animals[13,15] have culminated in the recent synthesis[17] of a new anti-coagulant. This substance, 3,3'-methylenebis(4-hydroxycoumarin), has practical advantages over heparin: it can be given orally and is relatively inexpensive. Its effectiveness and toxicity have not as yet been adequately studied. The object of this presentation is to determine the ability of this drug to act as an anticoagulant in humans and to ascertain its effectiveness and toxicity. An attempt has been made to formulate a satisfactory mode of administration and to assess in general the efficacy of such anticoagulant therapy in clinical practice.

Investigations of the action of 3,3'-methylenebis(4-hydroxycoumarin) in laboratory animals[2,4,13,15] have shown a prolongation of the clotting time and a reduction in prothrombin activity of the blood. Large or repeated toxic doses have been shown to produce widespread hemorrhage and in some animals death. Studies in humans[2,3,8,11,18] have been recorded in relatively few cases; not enough data is available to determine accurately the feasibility of administering this substance in clinical practice. We have therefore given this drug in repeated doses to a group of 71 adult patients.

Materials and Methods. The coagulation time was determined by a minor modification of the Lee and White two-tube method,[7] the average clotting time of the tubes being taken as the coagulation time. Normally, this varies from 8 to 14 minutes.

Prothrombin activity was measured by a modified Quick[10,12] technique using acetone-treated rabbit brain as the source of thromboplastin, 0.1 M sodium oxalate as the anticoagulant and 0.0125 M calcium chloride. The activity was expressed as a prothrombin index by the formula:

$$\text{Prothrombin index } \% = \frac{\text{Control plasma time (seconds)} \times 100}{\text{Pathologic plasma time (seconds)}}$$

The tests were performed on several dilutions (0.85% sodium chloride solution) of plasma, ranging from 62.5% to 25%. At these dilutions, significant changes in prothrombin activity are more readily detected than when undiluted plasma is tested. Normal control plasma was tested at the same time in the same dilutions.

Blood was drawn with minimal stasis in a syringe rinsed with 0.85%

* This includes any intravascular thrombosis or embolism such as bland or septic venous thrombosis, phlebitis migrans, thromboangiitis obliterans, arterial thrombosis or embolism in any organ.

† Since this manuscript was submitted a paper, "A New Practical Method for the Subcutaneous Administration of Heparin," was read by Leo Loewe and Philip Rosenblatt at the Clinical Research Meeting of the New York Academy of Medicine on May 27, 1943. They described a satisfactory technique for the use of heparin by the subcutaneous route. (This article will appear in a subsequent issue of this Journal.—EDITOR.)

sodium chloride solution. All glassware was washed with green soap and dichromate cleaning solution and thoroughly rinsed and dried. Scrupulously clean glassware must be used if reproducible results are to be obtained.

Of the 71 cases, 24 were females and 47 were males. The ages ranged from 20 to 70 years with half of the cases in the 50 to 60 year age group. The patients' weights varied from 100 to 200 pounds. The first 22 patients were selected only in so far as they could remain in the hospital for 2 weeks after the studies were started. They had a variety of diseases: 9 with arteriosclerotic heart disease; 3 chronic liver disease; 3, polycythemia vera; 2, generalized eczema; and the remaining 5 cases with varied clinical conditions. In the other 49 cases, there existed a clear-cut clinical indication for the use of an anti-coagulant. In this group are included 17 cases of pulmonary embolism and infarction, 9 cases of thrombophlebitis, 10 cases of peripheral arterial disease of varied etiology, 1 case of thrombosis of the central vein of the retina and 12 cases of embolus or thrombosis in a major artery.

Procedure. The 3,3'-methylenebis(4-hydroxycoumarin) was weighed out in gelatin capsules and was given orally on the average of 8 times to each patient. The doses varied from 200 to 500 mg. and the interval between doses varied from 1 to 7 days. The drug was administered on the first day the patient was studied. Because of the latent period of the action of the drug, which varies from 24 to 72 hours, at least two control readings of coagulation time and prothrombin index could be obtained in all cases. Blood was drawn for study at daily intervals whenever possible. In all, about 900 determinations were done, averaging 13 determinations per patient. The 10 cases of peripheral vascular disease were studied from 1 to 16 weeks. Most of the other cases were studied from 1 to 3 weeks. In these studies we have considered a satisfactory response to the dicoumarin to be an increase in the clotting time of the whole blood to between 15 and 20 minutes and a fall in the prothrombin index of the plasma to between 30% and 50%. At the same time there must not be untoward toxic effect, i. e., hemorrhagic manifestations.

Results. At first, the drug was used cautiously because of the toxicity in animals[2,4,13] and minor toxic effects reported in humans.[17] It soon became apparent however that single doses of 200 to 400 mg. could be tolerated. In general, the plan of dosage was directly dependent upon the individual response of the prothrombin index. The drug was given if necessary in daily doses of 200 to 500 mg. The drug was given in some cases when the prothrombin index was as low as 40%. Our more recent experience, however, is such that dicoumarin is not administered whenever the prothrombin index is less than 50%.

The results of 6 selected cases illustrating variation in response to the drug are shown in Figure 1. A single dose of 400 mg. is usually effective in producing the desired response.[18] Two similar cases, each of which received 500 mg. of the drug showed a marked difference in response: 1 showed a reduction in prothrombin activity and considerable prolongation of the coagulation time over a period of 1 week while in the other case the response was minimal.

Two other cases, essentially similar in age and weight, received approximately 2000 mg. of the dicoumarin in divided doses over an

18 day period. In 1 case the effect was marked and prolonged with evidence of toxicity. The prothrombin index fell to 10% of the normal and the coagulation time rose to 35 minutes. The effect persisted for 7 days after the drug was stopped. In the other, however, the effect was minimal and in no way comparable. The minimal prothrombin index in this instance was 40% while the maximal coagulation time was 20 minutes. Most of the determinations in this case were close to the normal range.

Toxic Effects. In 2 cases transient cramp-like abdominal pains and mild diarrhea occurred a few hours after ingestion of the drug. One of these patients complained of temporary crampy abdominal pains after each ingestion of the drug. Toxic manifestations of bleeding occurred in 8 cases, summarized in Table 1.

TABLE 1.—CASES SHOWING HEMORRHAGIC MANIFESTATIONS

Diagnosis	Dosage of dicoumarin	Prothrombin index at time of bleeding (%)	Site of bleeding and duration	Therapy to combat bleeding	Outcome
Eczema	1200 mg. in 12 days	21	Skin 7 days	None	Skin improved temporarily
Arteriosclerotic heart disease; renal calculus	2000 mg. in 18 days	13	Kidney 2 days	None	Recovery
Generalized arteriosclerosis	2400 mg. in 13 days	13	Kidney 7 days	3 blood transfusions	Fresh blood transfusions did not stop bleeding; recovery
Embolus to femoral artery	1000 mg. in 4 days	7	Amputation stump; rectum 11 days	5 blood transfusions	Death from hemorrhage
Pulmonary infarction; thrombophlebitis	2200 mg. in 13 days	10	Operative incision	5 blood transfusions	Fresh blood transfusions did not stop bleeding; recovery
Arterial embolus	1200 mg. in 7 days	20	Operative wound 5 days	2 blood transfusions	Fresh blood transfusions did not stop bleeding; recovery
Thromboangiitis obliterans	6000 mg. in 12 weeks	6	Gums 2 days	None	Recovery
Pulmonary infarction; thrombophlebitis	1800 mg. in 20 days	20	Lung 1 day	None	Recovery

Liver function tests such as the cephalin flocculation test, hippuric acid excretion test, bromsulphalein test, icterus index, and galactose tolerance test were performed in cases showing toxic effects. No interference with liver function could be demonstrated. Vitamin K had no effect on the circulating prothrombin or on the bleeding tendency. This parallels the experience of Bingham, Meyer and Pohle.[2]

Discussion. Our results show that oral administration of repeated doses of 3,3′-methylenebis(4-hydroxycoumarin) is effective in producing a variable and often marked prolongation of the coagulation time and a reduction in the prothrombin index. The mechanism of this action in decreasing the coagulability of the blood has been thought to be due to this reduction in the prothrombin activity.

In some of our cases, a marked reduction in prothrombin content of the plasma to 10% was not associated with an increase in the coagulation time. This corresponds to our findings in cases of obstruc-

tive jaundice not receiving the dicoumarin, in which a normal coagulation of the whole blood existed with low prothrombin content of the plasma. In many of the other cases receiving dicoumarin, however, elevations of the coagulation time to over 30 minutes were observed when the prothrombin activity fell to low levels (below 30%).
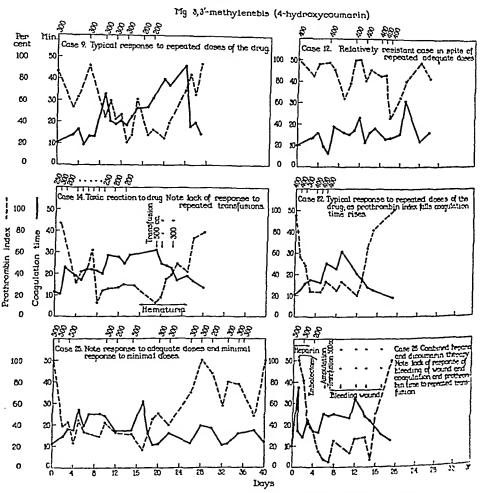
Fig. 1.—Variations in response to mg. 3,3' methylenebis(4-hydroxycoumarin)

All investigators are agreed that the coagulation defect occasionally seen in obstructive jaundice is a manifestation of an inadequate prothrombin content of the blood. The variable effect of dicoumarin upon coagulation and the differences which often exist between the coagulation defect after administration of this drug and in obstructive jaundice suggest the possibility that dicoumarin prolongs coagulation not only through a reduction in the prothrombin, but through other as yet undetermined effects. Though parenteral administration of vitamin K will restore the prothrombin to normal level in obstructive jaundice,

it has no effect upon the reduced prothrombin brought about by dicoumarin.

It is well established that prothrombin is formed in the liver and that the blood prothrombin falls when widespread liver disease is present or when the supply of vitamin K or its precursors is reduced. The fact that the lowered blood prothrombin following dicoumarin is not elevated by parenteral administration of vitamin K indicates that this vitamin is not directly implicated in the prothrombin deficiency. The remaining assumption, therefore, has been tentatively held, namely, that dicoumarin interferes with the elaboration by the liver of normal prothrombin. It should be emphasized, however, that there is no collateral evidence by various function tests that the dicoumarin affects liver function.*

Our experiences with this drug have led us to employ it in clinical states in which a disturbed coagulability of the blood might be of value. Because of the previously described latent period after the oral administration of the dicoumarin, we and others[11] have given heparin by the continuous intravenous route until the dicoumarin effect became evident. At this time a marked fall in prothrombin activity occurred. Heparin was then discontinued and repeated doses of the dicoumarin were prescribed in a manner similar to the illustrative cases of this communication. At the present writing we have used these drugs in combination in intra-arterial surgery, thrombosis or embolism of a large artery, pulmonary embolism, thrombophlebitis (septic and bland), thrombosis of the central vein of the retina, cavernous sinus thrombosis, thromboangiitis obliterans, phlebitis migrans and subacute bacterial endocarditis.

Our clinical experiences with 3,3'-methylenebis(4-hydroxycoumarin) have led us to certain preliminary conclusions. The individual variation of different patients is so great that a workable dosage schedule for administration cannot be definitely formulated. Many of the patients in whom prolongation of the coagulation time of the blood might prove desirable are acutely ill. If the action of the drug is to be effective, it should be capable of lowering the prothrombin content of the blood fairly rapidly. Trials with different doses are not feasible in such cases. This applies to the clinical situations in which pulmonary embolism, arterial embolism or thrombosis, arteriotomies and certain venous thrombotic states are implicated. The variability of effect of dicoumarin and the inability to predict its action greatly lower its possible usefulness in such conditions.

Similarly, we have occasionally produced an initial fall in prothrombin activity to about 40% of normal but have been unable to maintain this level during the entire period. Despite daily determinations of the prothrombin level of the blood and the fitting of each dose of the dicoumarin to the preceding prothrombin determination, we have not always been able to maintain the lowered levels evenly.

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* Since this manuscript was submitted for publication S. Shapiro, M. H. Redish and H. A. Campbell (Proc. Soc. Exp. Biol. and Med., 52, 12, 1943) have shown that vitamin K in large doses may correct the prothrombin deficiency resulting from minimal effective doses of dicoumarin in humans.

Several instances in which vascular thrombosis occurred during the course of dicoumarin administration may have been due to such temporary escapes during which time the prothrombin levels rose to normal values for 1 or 2 days. This sequence occurred in 1 case of postoperative pulmonary embolism in which massive thrombophlebitis in a lower extremity appeared about 1 week after dicoumarin administration was started. In other cases, however, thrombosis or embolism developed while the prothrombin activity was below 50%. Recurrence of venous extremity thrombosis was seen in 1 case of phlebitis migrans and embolic closure of the iliac artery occurred in a patient recovering from a recent myocardial infarction when the prothrombin content was 25% of normal. Another patient died suddenly probably from pulmonary embolism when the prothrombin was 20%. These observations have led us to question the theoretical grounds upon which anticoagulants are used.

We have observed postoperative bleeding in many cases when dicoumarin was administered either before operation or shortly thereafter. We have also noted a tendency to hemorrhage in any patient receiving dicoumarin in whom an unrelated lesion that might bleed was present. Examples of this include bleeding into the skin in a case of eczema, bleeding from the kidney in a patient with a renal calculus, bleeding from ulcers of the extremities in thromboangiitis obliterans, and bleeding into the pleural cavity following pneumothorax in a case of pulmonary tuberculosis. In regard to operative procedures, hemorrhage at the time of operation may occur only in patients who received the dicoumarin several days previously. If the drug is given on the day of operation, there is no such risk. However, in such cases secondary hemorrhage may occur early in the postoperative course when sutures, drains, or packings are disturbed. Bleeding in all these instances occurred when the prothrombin was less than 20% of the normal.

The 10 cases of occlusive peripheral arterial disease were carefully studied for 3 months. During this period the patients were ambulatory and were examined every other day. Dicoumarin was administered whenever the prothrombin level rose above 60%. Except for slight improvement in an ischemic ulcer of the foot, no beneficial effect of the drug could be observed. There was no essential change in the degree of intermittent claudication or coldness of the extremities in any of these cases during this period.

It should be stated, however, that the toxic effects previously described do not give a true picture of the degree, frequency and severity of toxicity that one should expect from clinical use. Thus the bleeding in 3 cases can be ascribed to over-zealous forcing of the drug in an effort to determine how much could be given. Although the desired effect on the coagulation time and prothrombin index had been produced earlier, drug administration was nevertheless continued.

The prothrombin and coagulation level at which bleeding is likely to occur seems to be between 20% and 5% for the former and over 25 minutes for the latter. The threshold for hemorrhage seems to be more closely related to the prothrombin content than to the coagula-

tion time. The hemorrhagic tendency, once developed, is likely to persist until the prothrombin index rises to 30% or more and the coagulation time falls below 20 minutes.

Four cases received repeated transfusions of fresh blood in an effort to elevate the circulating prothrombin and diminish the bleeding tendency. In none of these instances were dramatic effects observed, and we believe that bleeding ceased only after the dicoumarin effect had worn off and the prothrombin level had become elevated. In these cases it was apparent that transfusions served only to maintain the hemoglobin level and had but little effect on the cessation of bleeding. There was one death from hemorrhage despite 5 blood transfusions.

Our experiences with the effect of dicoumarin in promoting the healing of ulcers of the extremities due to arterial insufficiency are restricted. In 1 case of arteriosclerotic occlusive peripheral vascular disease with diabetes mellitus, slow healing of a large ulcer occurred over a 3 month period. During this time the plasma prothrombin was maintained between approximately 30% to 50%. Occasional oozing of blood from the ulcer occurred. At the termination of treatment, the ulcer was one-half its previous size and its base was granulating well. In another case, rapid healing of a refractory arteriosclerotic ulcer occurred within 2 weeks.

Plan of Therapy. The following therapeutic plan for prolongation of blood coagulation with 3,3'-methylenebis(4-hydroxycoumarin) may be found useful in certain instances. It is our present procedure to administer orally as the first dose 300 mg. to a patient weighing 130 pounds or less, or 400 mg. to one weighing over 160 pounds. On the second day, an additional 200 mg. is sometimes given. The subsequent doses will depend upon the results of the coagulation and prothrombin tests. It is imperative that prothrombin tests be performed daily. If no effect is observed by the third day, a dose of 300 mg. may be given. If a marked effect is observed, however, further administrations of the drug are withheld. Repeated doses, as much as 300 mg. or more daily, may be required in resistant cases. In other instances smaller doses at less frequent intervals are all that is required. Such a general scheme, in which dosage is controlled by tests performed at daily intervals, will enable one to exercise control.

Conclusions. 1. The oral administration of 3,3'-methylenebis(4-hydroxycoumarin) produces a marked fall (after a 24 to 72 hour latent period) in the prothrombin content and prolongation of the coagulation time of the blood in most cases.

2. There is great variability in the degree of response to this drug. A definite fixed dosage schedule cannot be made. Patients must be individualized.

3. Because of the variable response and latent period the drug has not always been useful in the therapy of arterial thrombosis or embolism, arteriotomy or major pulmonary embolism.

4. Because of the danger of hemorrhage, the drug has not proved useful during or shortly after operative procedures or in patients with unrelated lesions from which bleeding might occur.

5. Transfusions of fresh blood do not arrest the hemorrhagic tendency due to dicoumarin.

6. Several instances have been observed in which embolism, thrombosis or progression of existing venous thrombosis have occurred despite a low blood prothrombin induced by dicoumarin.

7. Symptomatic improvement in the 10 cases of occlusive peripheral vascular disease was not observed during a 3 month period while the prothrombin remained depressed as a result of dicoumarin administration.

8. It is possible that dicoumarin affects blood coagulation not only by lowering the prothrombin content, but through other mechanisms.

9. We believe that further trial of the drug is required before its effects in peripheral venous thrombosis and in pulmonary infarction can be determined.

10. dicoumarin should not be administered if the prothrombin index is less than 50%.

REFERENCES

1. Best, C. H.: Heparin and Thrombosis, The Harvey Lectures, p. 66, 1940-1941.
2. Bingham, J. B., Meyer, O. O., and Pohle, F. J.: Am. J. Med. Sci., 202, 563, 1941.
3. Butt, H. R., Allen, E. V., and Bollman, J. L.: Proc. Staff Meet. Mayo Clin., 16, 388, 1941.
4. Campbell, H. A., Smith, W. K., Roberts, W. L., and Link, K. P.: J. Biol. Chem., 138, 1, 1941.
5. Crafoord, C.: Acta chir. Scandin., 82, 319, 1939.
6. Jorpes, J. E.: Heparin, Oxford University Press, 1939.
7. Lee, R. I., and White, P. D.: Am. J. Med. Sci., 143, 495, 1913.
8. Meyer, O. O., Bingham, J. B., and Axelrod, V. H.: Am. J. Med. Sci., 204, 11, 1942.
9. Murray, D. E. W., and Best, C. H.: Ann. Surg., 108, 163, 1938.
10. Pohle, F. J., and Stewart, J. K.: Am. J. Med. Sci., 198, 623, 1939.
11. Prandoni, A. G., and Wright, I. S.: Presented before the New York Section of the Society for Experimental Biology and Medicine, November 20, 1941.
12. Quick, A. J.: J. Am. Med. Assn., 119, 1658, 1938.
13. Roderick, L. M., and Schalk, A. F.: North Dakota Agric. Exp. Sta. Bull., No. 250, 1931.
14. Roderick, L. M.: Am. J. Physiol., 96, 413, 1931.
15. Schofield, F. S.: Canad. Vet. Rec., 3, 74, 1922.
16. Schofield, F. S.: J. Am. Vet. Med. Assn., 64, 553, 1923-1924.
17. Stahmann, M. A., Huebner, C. F., and Link, K. P.: J. Biol. Chem., 138, 513, 1941.
18. Stats, D., and Bullowa, J. G. M.: Proc. Soc. Exp. Biol. and Med., 50, 66, 1942.

HEMATOPORPHYRINURIC NEURITIS

REPORT OF A CASE

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Of all the unusual conditions involving the nervous system which produce a neuritis, excluding those due to the heavy metals, vitamin deficiency, trauma or infection, there is none about which as little is known as hematoporphyrinuric neuritis. In this condition the neuritis

tends to be motor in nature, usually affecting the upper extremities, but often beginning in the lower extremities and ascending progressively to produce a clinical picture similar to Landry's paralysis. In many cases, the paralysis ascends to the medulla. This is followed by death from respiratory failure. Pathologically, the nerve involvement is not specific and in most cases reveals only the usual degenerative changes in the myelin sheaths and axons with degeneration or loss of anterior horn cells. Clinically, neuritis caused from hematoporphyria can be recognized because of its association with acute gastric symptoms such as colic and pains radiating into the loins. However, it must not be confused with lead colic, which is also often associated with neuritis. Unfortunately, little is known either about the cause of hematoporphyria or about the manner in which it affects the nerves.

Since the disease is often initiated by repeated acute colicky pain in the abdomen, it may first come to the attention of the surgeon or internist. However, the red or wine-colored urine may send the patient to the urologist, or the sensitivity of the skin to light and the formation of bullæ after exposure to sunlight[3] may bring the dermatologist into the picture. Muscular weakness and paralysis with occasional mental symptoms may involve the neuropsychiatrist before the condition is diagnosed. It is, therefore, a disease of general interest to every medical man. Because the disease is not well understood, study of individual cases should be of considerable value in furthering our knowledge of the meabtolism of pigments in the human body.

Case Report. F. U., a white male, aged 47, was first seen in consultation with Dr. Royal T. Liles at Touro Infirmary on August 11, 1942, in a semiconscious, moderately delirious condition, occasionally groaning with pain and apparently dehydrated. Muscular weakness of the extensors of the wrists and feet was obvious. He was apparently unable or unwilling to use his arms even when restlessly tossing about.

The patient had been nervous since he had had generalized abdominal pains in 1932 when a papilloma was removed from the bladder by transurethral fulguration. In 1940, he had such an acute attack of abdominal colic and discomfort that a laparotomy was done, but nothing was found except some adhesions. No information was obtainable as to whether the urine was discolored or whether there was any muscular weakness on that occasion, but shortly after the operation there appeared a transient paralysis of the left arm which lasted about 5 days. The abdominal symptoms were not relieved, and the patient continued to complain intermittently of colicky pains. Recently, this had become so acute that he was brought to the hospital. For several days prior to his admission he had been vomiting, especially after eating. Bowel movements remained regular until 2 days after admission when he began to have diarrhea, averaging 10 to 20 stools daily. These were unformed, moderately light-colored, and watery. The patient continued to have severe abdominal pains with delirium and progressive weakness of the extremities. Urinary retention developed, necessitating the insertion of an indwelling catheter into the bladder.

The patient had had the usual childhood diseases, and had had gonorrhea 10 years previously. He imbibed alcoholic beverages excessively, consuming approximately 1 pint a day for several years.

The family history was significant. A sister had died of an undiagnosed condition with abdominal colic and progressive neuritis at the age of 22. A brother had had a severe illness characterized by abdominal colic and weakness from which he had gradually recovered.

Examination of the patient upon admission revealed a blood pressure of 214/110, pulse 120 and temperature 99.4° F. The patient was lying on his back, apparently semiconscious, groaning faintly, restless and unable to coöperate with the examiner. All of the cranial nerves appeared normal except for the fundi, which showed moderate sclerosis of the vessels. The teeth were not discolored. The tongue was shining and purplish red in color. Motor weakness of both upper and lower extremities was obvious and wrist drop was apparent. Sensation could not be tested satisfactorily. There were no other abnormal physical findings except for an old healed right rectal incision. There were no masses in the abdomen, and tenderness in this region could not be elicited.

Roentgenograms of the chest on August 11, 1942, were negative. A gastro-intestinal series showed hyperperistalsis with distention of both small and large bowel loops.

On admission, July 30, 1942, the red blood cell count was 5,100,000 with 80% hemoglobin and the white blood cell count was 7900 with 71% polymorphonuclear cells. Urinalysis was negative. On July 31, 1942, the non-protein nitrogen was 42.9 and dextrose 100. Wassermann reaction was negative. On August 7, 1942, the white blood cell count had increased to 12,500 with 75% polymorphonuclear cells. The urine showed hyaline casts. Stools were negative for parasites and ova. On August 11, 1942, the urine was wine-colored and showed a positive urobilinogen of 1:258 and a positive test for uroporphyrin, Type 1. On August 12, 1942, the non-protein nitrogen had risen to 66. Plasma sodium chloride was 482 and carbon dioxide combining power 33.4. All febrile agglutinations were negative. Blood cultures were negative.

From the day of admission on July 30, 1942, abdominal colic was constant. On August 7, the patient had 25 bowel movements with much tenesmus. The temperature was 101° F. On August 9, diarrhea was still present, but the temperature had gone down. On this day extreme weakness of the left arm and both legs was evident. On August 11, urinary retention developed and the patient was catheterized. A dark red wine-colored urine was obtained. On August 12, 1942, the patient began to show bulbar symptoms, having obvious difficulty in coughing and swallowing. He was placed in an oxygen tent. On August 13, 1942, he became cyanotic, and there was evidence of respiratory paralysis. He was placed in a respirator, but expired the same day.

Findings at Autopsy. A complete autopsy was performed on August 14, 1942, but only the pathologic findings which were a—

ciated with the condition which contributed directly to the patient's death will be discussed.

Gross Pathology of the Brain and Spinal Cord. No evidence of thrombosis was noted in the superior sagittal sinus. The dura stripped with ease from the pia arachnoid and no subdural hemorrhages were noted. The pia arachnoid was grayish white in appearance and in scattered areas over the cerebral hemispheres showed areas of thickening which varied in size from 1 to 5 cm. in diameter. The brain was removed and sectioned. No flattening of the cerebral gyri was noted. Serial sections made through the cerebral hemisphere showed no evidence of gross pathologic changes. No changes were noted in the cerebellum except for some gelatinous degeneration of the dentate nucleus. The spinal cord was removed by the anterior approach and serial sections through this showed no evidence of gross pathologic changes. The leptomeninges over the sulci of the frontal and parietal lobes were thickened and fibrosed. There were worm-like areas of depressed and narrowed convolutions of the cortex over the frontal and parietal lobes bilaterally. A slight degree of arteriosclerosis of the basal vessels of the brain was present.

The pathologist reported the following anatomic diagnoses: cardiac hypertrophy; pulmonary atelectasis; acute ulcerative colitis; benign nephrosclerosis; chronic peritonitis; focal cortical atrophy; leptomeningeal fibrosis; and cerebral arteriosclerosis (mild).

Spectroscopic examination of the urine revealed the presence of uroporphyrin, Type 1.

Microscopic Findings of Brain. The leptomeninges were greatly thickened and contained large numbers of fibroblasts. Many of these were filled with a yellow pigment. There were also numerous macrophages present in this tissue and some of these were also filled with the same pigment. A few free red cells were seen in the subarachnoid space over the medulla. There was a patchy loss of ganglion cells in the cortex. Many of the remaining cells were edematous. The ependymal lining was intact, but there was a patchy subependymal gliosis. In the white matter there were patches of glial scarring and many *Corpora amylocca*. There was a pronounced Monckeberg's sclerosis of the internal capsule and basal ganglia. The arterioles of the subarachnoid space over the cerebellum showed considerable hyalinization.

Additional microscopic diagnoses included myocardial scars, acute cholangitis, fibrosis of leptomeninges, focal cerebral atrophy, Monckeberg's sclerosis of cerebrum and arteriolar hyalinization, subarachnoid space.

Pathologist's Comment. This is fundamentally a case of hematoporphyrinuria, the cause of which is not known. There was no history of having taken any of the drugs such as trional or veronal which, it is believed, may predispose to this condition. As is usual in these cases, no significant visceral lesions were found. It is quite probable that the lesions in the colon were of a terminal nature and were associated with the uremia. It does not seem likely that the mucosal

lesions were present at the time of the roentgenographic examination inasmuch as they were all of a very recent nature. However, the colon could have been distorted because of adhesions.

Comment. Hematoporphyria is rarely seen in man. By 1940 less than 200 cases had been reported in the literature. The condition affects women more often than men and the initial attack usually occurs in the fourth or fifth decade. There may or may not be a familial history. The disease appears to be a metabolic disturbance intimately connected with hemoglobin synthesis and degradation, and is usually associated with the excessive excretion of porphyrin by the urine (porphyrinuria). Porphyrinuria is often so great that the abnormal wine color of the urine leads to its diagnosis.

First recognized by Gunther in 1911, this disease was later classified by him into three types: (1) congenital hematoporphyria;[5] (2) acute idiopathic hematoporphyria;[3] and (3) acute toxic hematoporphyria (due to lead, veronal, sulfonal and other barbiturates).[2] Up to 1940 less than 30 cases of the first type had been reported, 46 of the second type and about 100 of the third. In health, the urine, feces and bile contain traces of a porphyrin, but in porphyrinuria there is an abnormal excretion of this substance in the urine. The feces may contain porphyrin (coproporphyrin) and the intestine may also be the site of degradation products of hemoglobin, protoporphyrin and deuteroporphyrin. These are all related pigment substances.

Hematoporphyria is characterized by a fairly acute onset of severe, cramplike, abdominal pain which may radiate down to the thighs and flanks or even up to the chest. Nervousness, exhaustion, emotional instability or insomnia may precede the initial attack by weeks or even months. Nausea and vomiting may be associated with the abdominal pain. Although these patients usually do complain of constipation, this is not necessarily true. Convulsions and states of delirium may develop during the attack. There may be weakness of the extremities of a motor type which may ascend to involve the medulla, and this may be associated with dysphagia and respiratory paralysis. As a general rule, as the symptoms rapidly increase in severity, the visceral pains and distention often lead to a mistaken diagnosis and subsequent laparotomy. An increase in pulse rate, mild fever, moderate leukocytosis, urinary retention, toxic delirium, excitement or hallucinations may confuse the picture. The patient may complain of continued pains and paresthesias in the extremities, associated with weakness of the distal extensors. Reduced or absent tendon jerks may disclose a progressive multiple neuritis. The proximal or peripheral muscle groups may be affected, and objective sensory changes may or may not be found. Of particular interest are those cases that show an acute ascending form of paralysis which finally produces bulbar paralysis usually with a fatal outcome.[1] Approximately 50% of patients succumb to the first acute attack.

Roentgenograms usually reveal dilatation of some part of the intestinal tract, often of the large bowel. The urine is characteristically brownish-red or burgundy wine in color and contains large amounts

of porphyrin recognized by spectroscopic examination. Spinal fluid has been found normal in several cases, though pathologically it is not characteristic.

Acute degenerative lesions may be found in the peripheral nerves and in the spinal cord. The ventral horns may show swelling, eccentric nuclei or complete disappearance. The nerves and spinal roots may show disintegrated axons and myelin sheath degeneration. In general, the pathologic changes are of a parenchymatous toxidegenerative type.

REFERENCES

1. COURVILLE, C., and MASON, V. R.: Arch. Neurol. and Psychiat., **25**, 848, 1931.
2. CRAWFORD, H.: Med. J. Australia, **1**, 589, 1933.
3. NEWMAN, C.: Proc. Roy. Soc. Med., **29**, 47, 1935.
4. PALMER, H. W.: Ann. Int. Med., **13**, 1501, 1940.
5. PEACHY, C. H., DOBRINER, K., and STRAIN, W. H.: New York State J. Med., **38**, 848, 1938.

CARBON DIOXIDE BY INHALATION AS AN EXPECTORANT

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In 1905 Haldane and Priestly[12] first demonstrated that the carbon dioxide of the blood normally controls respiration. Shortly thereafter Henderson[14] expounded the rôle of carbon dioxide as a respiratory stimulant. In a large series of subsequent publications Henderson[15] advocated the therapeutic application of carbon dioxide by inhalation after anesthesia and surgical operations, in the treatment of carbon monoxide poisoning, whooping cough, asphyxia of the newborn, resuscitation from drowning, severe electric shock, morphine poisoning, and failure of the respiration from various other causes. Henderson recommended the inhalation of carbon dioxide for the purpose of controlling the respiration during anesthesia and for the prevention of the depression of the respiratory center in deep anesthesia. He attributed the development of postoperative atelectasis to the lowered tonus of the respiratory muscles of the thorax, particularly the diaphragm, caused by the anesthesia and by the postoperative depression of vitality. The diminished tonus of the respiratory muscles leads to an incomplete expansion of the thoracic cavity during inspiration. Thus the lungs are underinflated and bronchi or bronchioles become easily obstructed by accumulated mucus. Subsequent to such occlusion the air is gradually absorbed from the occluded area that, consequently, becomes atelectatic. This area represents a predilectional place for the development of postoperative pneumonia. Inhalation of carbon dioxide is capable of producing an increased tonus in the respiratory muscles and

thus of reëstablishing the normal inflation of the lungs; consequently it acts as a powerful preventative against postoperative atelectasis and pneumonia. Excellent results were noted by MacKenzie[20] with the use of carbon dioxide for deëtherization and for the prevention and treatment of postoperative atelectasis and pneumonia in 5000 cases. Scott and Cutler[24] recommended the inhalation of carbon dioxide in all patients operated on under general anesthesia and advised the administration of 30% carbon dioxide and 70% oxygen in addition to the air breathed for periods of about 1 minute at a time, interspersed with rest periods of about 2 minutes, at the end of the operation. Henderson and Haggard[16] attributed the beneficial effect of carbon dioxide inhalation in carbon monoxide poisoning to the stimulation of the respiratory center that is followed by vigorous respirations which serve the rapid elimination of the carbon monoxide from the system. Its use for resuscitation of the newborn was recommended on the basis that carbon dioxide is quite as effective a stimulant of the respiration in the non-breathing or poorly breathing infant as it is in carbon monoxide poisoning. Similarly intense depression of the neuro-respiratory system in morphine poisoning can be counteracted effectively by the stimulating effect of carbon dioxide. Hunter and Mudd[18] and Robinson and Selesnick[23] found that patients with alcoholic coma can be rapidly revived. Also Henderson[15] suggested carbon dioxide inhalations for the treatment of cyanide poisoning, particularly if the poison has been absorbed through the lungs. Hurst[19] and Campbell and Poulton[7] reported favorable results from carbon dioxide inhalations in bronchial asthma. Churchill[9] used the Henderson inhaler for the administration of carbon dioxide for aiding the reëxpansion of the lung in patients who were operated on for empyema. He found that this method was superior to blowing or breathing exercise. Striking results were observed by this procedure by Alison[1] in the treatment of acute bronchitis. He administered a mixture of carbon dioxide and oxygen in a tent for 15 minutes every hour.

The various physiologic responses to the inhalation of carbon dioxide have been extensively studied. Prinzmetal[22] found that the inhalation of 10% carbon dioxide in dogs rendered the intrapleural pressure more negative: from −4.5 to −8, and simultaneously increased the inspiratory chest circumference. By the inhalations of concentrations higher than 10% the intrapleural pressure not only becomes more negative on inspiration but also much more positive on expiration. Grueneberg and Viethen[11] recorded their observations in children from 3 weeks to 14 years of age: the effect of the inhalation of 1% carbon dioxide began in 6 minutes and consisted of an increase in the respiratory volume by 33 to 50%; 2% carbon dioxide began to act in the third minute, and 3% carbon dioxide in the second minute; by the inhalation of 4% carbon dioxide not only the respiratory volume was increased to 100% but also the respiratory rate. Concentrations of carbon dioxide from 5 to 10% increased the respiratory volume to 150 to 190%. They noted that the respirations returned to the pretreatment rate and volume in 2 minutes after the inhalations were discontinued, and

also that if higher concentrations were given with brief intermissions the respiratory center became more sensitive to lower concentrations of carbon dioxide. Similar observations were made by Hitzenberger.[17] The observations of Heller and his associates[13] are of significance from the standpoint of the practical application of this method of treatment. They used 5 and 7% carbon dioxide in air and found that in young healthy adults the respiratory minute volume was increased from 10 to 15 liters to 40 liters by 5% carbon dioxide and to 62 liters by 7% carbon dioxide. The response was variable in different subjects: although the respiratory stimulation was usually vigorous, there were some persons who showed only slight response in minute volume increase to 5 and even to 7% carbon dioxide. Also, there was a fair amount of variation in the same person on different days. Brown[5] observed that in healthy man the maximum stimulation of the respiratory center can be attained by the inhalation of 10.4% carbon dioxide.

Inhalation of carbon dioxide affects the bronchial tract directly and indirectly. Passive motion of the bronchial branches was observed by Macklin[21] following the instillation of iodized oil. Gordonoff[10] studied kymograms of the bronchographed lung. He found that the motion of the bronchi is synchronous with that of the ribs and the diaphragm. Castex and his associates[8] recently described active movements of the bronchi during consecutive phases of the respiratory cycle that were visualized with the aid of bronchocinematography. These active movements consist of changes in the length and caliber of the bronchi, peristalsis, undulation and torsion. The normal bronchi are elongated and dilated during inspiration and shortened and narrowed during expiration. Brunn and Brill[6] and Brown[4] observed the effect of carbon dioxide inhalation upon the bronchial tract during bronchoscopy. They report that the administration of carbon dioxide produced: (1) an increase in the rate and depth of respirations; (2) violent movements in the tracheobronchial tree and alterations in the shape of the lumina of its branches, thereby tending to free adherent mucus; (3) blanching of the mucous membrane of the trachea and bronchi.

We began the clinical use of carbon dioxide inhalations in tuberculous patients in 1930 and reported some of our observations in previous publications.[2] We were prompted by the favorable experience of others in various pulmonary diseases and by the difficulties often encountered in the management of cough in tuberculous patients. There are a great many cases of chronic pulmonary tuberculosis in which the well known expectorants fail to bring relief. The reasons for this are several: (1) the inflammatory exudate accumulating in the bronchial tubes may be too viscid and tenacious; (2) a dense mucopurulent plug may obstruct the way of free drainage from the bronchi; (3) the lung may be in a stage of subventilation. It has been pointed out by several investigators that without adequate inflation of the lung no adequate expectoration is possible: the air compressed by the diaphragm and the chest muscles represents the only agency that

actually expels inflammatory products from the bronchi at the moment when the previously tightly closed epiglottis suddenly opens. Subventilation with its consequent predilection to insufficient cough may be brought about by various factors such as reflex spasm of the thoracic muscles due to pleural pain, general debility, and diminished irritability of the respiratory center to normal stimuli. Furthermore, obstruction of branches of the bronchial tract may prevent the access of air to sections of the lung distal to the point of obstruction, thus rendering impossible the elimination of inflammatory exudate by coughing from this part of the lung. During the course of pulmonary tuberculosis such bronchial obstruction may be caused not only by a thick, viscid, mucopurulent plug, but also by inflammatory edema and swelling of the mucous membrane, bronchospasm, overgrowth of granulation tissue, kinking, deformity or collapse of the bronchus due to ulcer formation or bronchiectasis, and by fibrous bronchostenosis that may become easily occluded by even small amounts of mucus.

The use of opiates is universal for the treatment of cough during the protracted course of pulmonary tuberculosis. Their merit in controlling certain types of cough has been firmly established. Still, one should keep in mind that by their use the normal peristaltic movements of the bronchi and the full action of the ciliary epithelium are decreased or abolished. Such effect of the opiates in case of accumulation of mucopurulent tuberculous exudate in the bronchial tract would actually create a vicious circle by impeding bronchial drainage. To avoid such paradoxical situation it is advisable to use narcotics discriminatingly in the management of cough. Indeed, the rational treatment of cough should be directed against its cause; and if its cause lies in the presence of abnormal amounts of mucopus in the bronchi, the adequate evacuation and cleansing of the bronchial tract should be the primary objective. Only when this is accomplished should one resort to narcotics as adjuncts.

Method. The apparatus used in our work consists of a tank, containing a mixture of 10% carbon dioxide and 90% oxygen, mounted on a small platform on casters that makes it possible to give the inhalations to bed patients. An oxymeter regulates the flow of gas per minute. Originally we used an ordinary mask used for general anesthesia; more recently the B.L.B. mask is being used. The inhaler is connected to the tank by a rubber tubing. A rubber bag which serves as a small reservoir is attached to the inhaler. In some patients it was found expedient to give the inhalations through a glass tube instead of the mask; either because they were reluctant to accept the mask, or the respiratory stimulation was too strong from closed inhalation of the mixture. It is fully realized that, when inhalations are administered through a glass tube held in the patient's mouth, the admixture of air and dilution of carbon dioxide take place; but results by this so-called open method are quite satisfactory. The open method is recommended for patients who are markedly debilitated or who show some of the possible side-effects when the closed inhaler is used. It is a good policy to explain to the patient briefly the mode of action of the inhaled gas, and the expected changes in respiration, and the probable subjective symptoms. Inhalations by the closed method are given by a nurse. After proper instructions, inhalations through a glass tube can be administered without constant supervision; however, it is the responsibility of the nurse to regulate the flow of the gas, and time of the treatment. As a

rule, the meter is set to 4 to 5 liters per minute for closed inhalations and to 5 to 7 liters per minute for the open method. The length of each treatment varies from 5 to 15 minutes; and the inhalations are administered once, twice, or three times a day. It is necessary to observe the patient closely during the first treatment. His respiratory response and subjective reactions determine the conduct of further treatments. Since a self-experiment on one of us (A.L.B.) by the closed method, we fully appreciate the sensation experienced by the patient when marked inspiratory expansions of the chest are induced by carbon dioxide. They are conscious of breathing deeper and subsequent to the treatment they describe their experience in such terms as "the chest feels clear and cool" and "the chest feels so much lighter." If it is noted that the respirations become too strenuous, the inhalations should be given with brief (1 minute) interruptions. In rare instances, when the closed method is used, it may be necessary to reduce the flow to less than 4 liters per minute. Most patients appear quite comfortable, as if in euphoria. The latter can be explained: (1) by the presence of 90% oxygen in the gas mixture that is bound to counteract anoxemia; (2) by loosening up mucopurulent bronchial plugs and obstructive sticky, tenacious inflammatory exudate: the access of air is secured to underinflated regions of the lung; (3) by increased inspiratory expansion of the chest wall and by increased descent of the diaphragm atelectatic areas are stretched out and become aërated. In some of our patients we noted some transient minor side-effects of carbon dioxide inhalations such as hot sensations, palpitation, weakness, frontal headache, and slight dizziness. None of these symptoms interfered with the treatment when proper adjustments were made in the method of administration. In the beginning, the treatments are given daily; subsequently, the frequency of inhalations can be reduced, depending upon the relief obtained. Some patients were obliged to take them daily for an extended period of time, while in others the interval between inhalations could be increased to a week or even to 11 days. Carbon dioxide is an effective therapeutic agent, and in its use utmost individualization is required.

The retention of infected exudate in the bronchial tract harbors serious consequences: (1) the production of atelectasis; (2) the absorption of inflammatory products that may lead to constitutional symptoms; (3) the intracanalicular spread of the disease; (4) by its check-valve action may lead to the development of blocked cavities. It is also obvious that excessive, unproductive cough interferes with the general rest of the patient, and particularly with the rest of the diseased lung; it may handicap the approximation of cavity walls and the closure of cavities, and choking spells, vomiting, headache and insomnia may be its disagreeable consequences. Furthermore, excessive cough may accelerate the development of emphysema, may cause dyspnea, cyanosis, thoracic pain, and spraying of infected material from one part of the lung to the other.

In carbon dioxide by inhalation we have a most efficient expectorant at our disposal. With its aid we are able to change an excessive yet unproductive cough into a useful cough and thereby eliminate dangers inherent to the accumulation, retention, and insufficient expectoration of inflammatory products. According to our experience carbon dioxide liquefies the mucopurulent exudate in the bronchi and reduces its viscosity so that the sputum becomes thinner, more serous and watery; furthermore, the sputum is loosened up and consequently it is expectorated without strain or effort. The prompt relief obtainable by this treatment is best expressed in the comments of patients: "the cough

is not so dry, it is loose," "the cough does not jar me any more," "the cough is less, and not tight as before," "I do not have to exert myself when coughing," "I have no more dry spells of coughing," etc.

We have noted that following inhalations the amount of expectorated sputum is greater than before treatment, and also that adequate evacuation of the bronchi insures for the patient comparatively long periods of rest free of the annoying cough. Incidental by-effects of the satisfactory pulmonary drainage by carbon dioxide are: relief from dyspnea, undisturbed sleep during night, and improvement in the general subjective feeling. Often patients remarked how a feeling of pressure and heaviness was relieved by the treatment, that following inhalations their chest felt freer "like a loose sponge," and how much easier they were able to move about. Also we have noted the disappearance of chest noises and pharyngeal cough irritation.

When satisfactory evacuation of the bronchi has been accomplished, the amount of sputum becomes gradually less, unless further mucopurulent accumulation takes place during the interval between treatments. It can be seen, therefore, that the frequency of inhalations and gas flow per minute have to be individualized and adapted to the changing requirements of the patient. We have found that the inhalation of carbon dioxide not only alleviates distressing cough but also enables one to reduce the consumption of narcotics and expectorant drugs.

The recent painstaking investigations of Basch, Holinger and Poncher[3] concerning the effectiveness of carbon dioxide and of the commonly used expectorants confirm our own clinical findings. They studied the influence of ammonium chloride, potassium iodide, fluid extract of senega, fluid extract of ipecac, and emetine hydrochloride, and compared it with the effect of carbon dioxide. They found that carbon dioxide acts as a real expectorant by diluting the sputum — that is, by lowering its viscosity and reducing its solid contents. They state that in comparing the physical and chemical properties of the sputum after the use of carbon dioxide inhalations with the same properties after the administration of drugs one at once realizes the greater liquefaction of the sputum caused by carbon dioxide: "since in this treatment there is no interference with the chemical properties of the sputum through the secretion of the administered drugs into it, the dried residue, the amount of ash and the total nitrogen content are regularly markedly lowered."

As to the selection of cases for this treatment, it is indicated whenever there is an accumulation and retention of inflammatory exudate in the bronchial tract and its evacuation — in spite of strenuous cough — is inadequate. There are patients that should not be given this treatment: (1) patients with recent pulmonary hemorrhage; (2) those with marked emphysema; (3) when widespread pulmonary fibrosis is present without atelectasis, bronchiectasis or mucopurulent retention in the air-passages; (4) cases of acute plastic pleurisy and pleurisy with effusion; (5) hypertensive patients; and (6) when the cause of cough is outside of the lungs.

Conclusions.   From our experience with this method of treatment during the past twelve years we have arrived at the following conclusions:

1. Carbon dioxide by inhalation is a most efficient expectorant.

2. When a mixture of 10% carbon dioxide and 90% oxygen is administered by the closed method, through a B.L.B. mask, or by the open method, through a glass tube, it is tolerated by the patients well. Occasional minor by-effects do not interfere with the treatment.

3. The amount of gas mixture given and the frequency of treatments should be adapted to the individual case.

4. The relief obtained by the inhalations of carbon dioxide is noticed subjectively and objectively: (a) spells of strenuous, exhausting coughing are prevented and thereby rest is secured for the patients and particularly for the lungs; (b) an unproductive cough is transformed into a useful one; (c) directly after inhalation the amount of expectorated sputum is increased and its character changes from a heavy, thick and tenacious type into a thinner, serous and more watery kind; (d) the use of expectorant drugs and narcotics can be reduced.

5. The effectiveness of carbon dioxide is attributable mainly to the following factors: (a) it is a powerful respiratory stimulant and induces increased inspiratory movements of the thorax that, in turn, cause a stretching and dilatation of the bronchial tubes; (b) it stimulates the myo-elastic structures of the lung and leads to a forceful peristaltic movement of the bronchi; (c) it liquefies mucopurulent inflammatory exudate that stagnates in the bronchial tract.

REFERENCES

1. ALISON, J. F.:   South. Med. J., 25, 386, 1932.
2. BANYAI, A. L.:   Am. Rev. Tuberc., 30, 642, 1937; Tubercle, 19, 468, 1938; Dis. of Chest, 4, 8, 1938.
3. BASCH, F. P., HOLINGER, P., and PONCHER, H. G.:   Am. J. Dis. Child., 62, 981, 1149, 1941.
4. BROWN, A. L.:   J. Am. Med. Assn., 95, 100, 1930.
5. BROWN, E. W.:   U. S. Navy Med. Bull., 28, 523, 1930.
6. BRUNN, H., and BRILL, S.:   Ann. Surg., 92, 801, 1930.
7. CAMPBELL, A., and POULTON, E. P.:   Oxygen and Carbon Dioxide Therapy, Oxford Univ. Press, 1938.
8. CASTEX, M. R., MAZZEI, E. S., and MALENCHINI, M.:   Arch. arg. enf. d. ap. rex. y tuberc., 9, 307, 1941.
9. CHURCHILL, E. D.:   Boston Med. and Surg. J., 194, 623, 1926.
10. GORDONOFF, T.:   Ztschr. f. d. ges. exper. Med., 97, 1, 1935.
11. GRUENEBERG, F., and VIENTHEN, A.:   Jahrb. f. Kinderh., 128, 65, 1930.
12. HALDANE, J. S., and PRIESTLY, J. G.:   J. Physiol., 32, 225, 1905; Respiration, London, Oxford Univ. Press, 1935.
13. HELLER, E., KILLISCH, W., and DRINKER, C. K.:   J. Indust. Hyg., 11, 293, 1929.
14. HENDERSON, Y.:   Brit. Med. J., 2, 1812, 1906.
15. HENDERSON, Y.:   J. Am. Med. Assn., 103, 750, 1934, and 108, 471, 1937; 99, 654, 1932; Comprehensive Bibliography in Adventures in Respiration, Baltimore, Williams & Wilkins, 1938.
16. HENDERSON, Y., and HAGGARD, H. W.:   J. Am. Med. Assn., 77, 1065, 1921.
17. HITZENBERGER, K.:   Wien. klin. Wchnschr., 45, 276, 1932.
18. HUNTER, F. T., and MUDD, S. G.:   Boston Med. and Surg. J., 190, 971, 1924.
19. HURST, A. F.:   J. Laryngol. and Otol., 46, 413, 1931.
20. MACKENZIE, J. R.:   Brit. Med. J., 1, 561, 1932.
21. MACKLIN, C. C.:   Am. Rev. Tuberc., 25, 393, 1932.
22. PRINZMETAL, M., BRILL, S., and LEAKE, C. D.:   Proc. Soc. Exper. Biol. and Med., 28, 832, 1931.
23. ROBINSON, L. J., and SELESNICK, S.:   J. Am. Med. Assn., 105, 1734, 1935.
24. SCOTT, M. W. J., and CUTLER, E. C.:   J. Am. Med. Assn., 90, 1, 1928.

THE MAZZINI SLIDE FLOCCULATION TEST—SENSITIVITY OF ITS ANTIGEN

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THE value of a laboratory test often depends on its variability and stability under different conditions. Thus with the Mazzini flocculation test for syphilis as well as with other tests for syphilis, there is a minimum and maximum degree of sensitivity of its antigen according to its age.

When properly prepared and used, this antigen gives reliable results comparable to many of the established, more complicated and more difficult tests which have stood the test of time.

In the 1941 Original Methods Survey of tests for Syphilis conducted by the U. S. Public Health Service,[2] the Mazzini test was found to have a specificity of 99.6 in normal and non-syphilitic bloods and a specificity of 95.8 in all bloods including leprosy and malaria. The sensitivity was found to be 78.6 in all syphilitic bloods, including early, treated and latent cases.

The Mazzini Test.[1] The Mazzini antigen is prepared by the alcohol and ether extraction of beef heart powder and powdered egg yolk. The acetone insoluble lipoids are added, and the antigen is cholesterinized on the basis of a previous titration. To prepare the final suspension, 0.4 cc. of the cholesterinized antigen is added to 3 cc. of normal saline solution buffered at a pH of 6.3 to 6.4. The suspension is shaken for 10 seconds and then allowed to stand at room temperature for 3 to 4 hours at which time it reaches its maximum sensitivity. For emergencies Mazzini recommends that the antigen be ripened in a refrigerator at 6° to 8° C. for 15 minutes.

The suspension is drawn into a 5 cc. syringe fitted with a 25-gauge needle. To 0.05 cc. of serum on a slide, 1 drop of antigen is added from the syringe. The slide is rotated for 4 minutes and the results are read under low-power magnification. Either paraffin or sealing wax rings may be used on the slides.

Mazzini attributes the specificity and increased sensitivity of his test to the use of egg yolk, the lipoid-cholesterin ratio, the serum-antigen ratio, and the concentration of the hydrogen ion in the final suspension.

Experimental Material.—Because this test has shown an increased sensitivity correlated with a high specificity, and since it is a quick and easily performed test, it is adaptable for testing blood donors. In this connection we wished to know whether the antigen should be prepared whenever needed by ripening it in the refrigerator for 15 minutes or whether it would have as great a sensitivity if made once a day and used for 27 to 28 hours, thereby allowing a single preparation of antigen each day.

For this purpose we employed 4 types of antigen suspensions: (1) suspensions which had stood 4 hours at room temperature; (2) suspensions which had been refrigerated 6° to 8° C. for 15 minutes; (3) suspensions which had been refrigerated for 15 minutes at 6° to 8° C. followed by 1 hour at room temperature; and (4) suspensions which had stood from 27 to 28 hours at room temperature. These antigens were tested against unknown sera and known syphilitic sera from patients in various stages of infection.

One series was done during the winter at room temperature of approximately 73° F. and another during the summer with the temperature in the serology laboratory ranging from 80° to 94° F.

Winter Series. When the specificity of the 4 types of antigen suspension was compared, it was found that out of 340 sera negative with the 4 hour antigen only one showed a doubtful reaction, which was with the 27 to 28 hour antigen. This was not of statistical significance.

When the sensitivity of these 4 types of antigen suspensions was compared it was found that 103 sera showed reactions with the 4 hour antigen, 94 reacted with the 27 to 28 hour antigen, 74 reacted with the 15 minute refrigerated antigen, and 85 reacted with the antigen which had been refrigerated for 15 minutes and then allowed to stand 1 hour at room temperature. This is graphically illustrated in Figure 1.
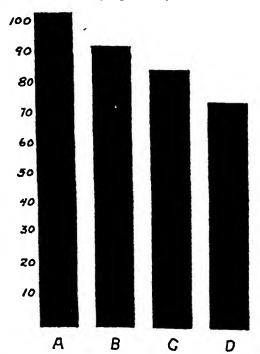
FIG. 1.—Comparison of antigens and number of reactions—winter series. *A*, 4 hour antigen, *B*, 27–28 hour antigen; *C*, antigen refrigerated 15 minutes plus one hour at room temperature; *D*, antigen refrigerated 15 minutes.

The statistical method of analysis was used to determine whether the difference among the results is significant when based upon a sample of this size. The formula for the standard error of the difference between two percentages $\left(\sqrt{\frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}} \right)$ * was employed.

* p = % of occurrence; q = % of non-occurrence; n = number in the sample.

When the 27 to 28 hour antigen suspension, which failed to react 9 times (8.7%) was compared with the antigen suspension refrigerated for 15 minutes, which failed to react 29 times (28.9%), the standard error of the difference was 5.39 and the difference was more than 3 times the standard error. Since, when the difference is 3 times the standard error, data are considered statistically significant, it could be concluded that the sample was large enough to establish the superiority of the 27 to 28 hour antigen over the antigen refrigerated for 15 minutes.

The 9 sera which failed to react with the 27 to 28 hour antigen suspension showed negative standard and presumptive Kahn reactions, and none of them gave more than a doubtful reaction with the 4 hour antigen. One serum which showed positive Kahn Standard and Presumptive tests and a doubtful Mazzini failed to react with the 15 minute refrigerated antigen.
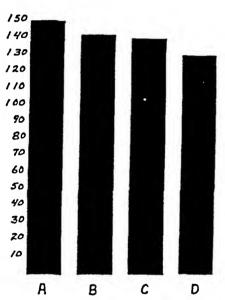
FIG. 2.—Comparison of antigens and number of reactions—summer series. A, 4 hour antigen; B, 27–28 hour antigen; C, antigen refrigerated 15 minutes plus one hour at room temperature; D, antigen refrigerated 15 minutes.

When the 27 to 28 hour antigen suspension and the antigen suspension ripened for 15 minutes in the refrigerator plus 1 hour at room temperature which failed to react 18 times (17.5%), were compared, the standard error of the difference was 4.8, and the number of standard errors contained in the difference was less than 2. Therefore, the sample was not large enough to establish the superiority of the 27 to 28 hour antigen over the antigen refrigerated for 15 minutes plus 1 hour at room temperature.

When the 27 to 28 hour antigen suspension was compared with the 4 hour antigen the standard error of the difference was 2.87, and the number of standard errors in the difference was more than 5. There

fore, the conclusion could be drawn that the 4 hour antigen suspension was the most sensitive.

Summer Series. The same 4 types of antigen suspensions used in the winter were tested during the summer at room temperatures.

When the specificity of these antigens was compared, it was found that out of 133 sera reacting negatively with the 4 hour antigen suspension only 1 showed a doubtful reaction and that was with the 27 to 28 hour antigen suspension.

When the sensitivity of the 4 types of antigen suspensions was compared in the summer series it was found that 150 sera showed reactions with the 4 hour antigen suspension, 144 reacted with the 27 to 28 hour antigen suspension, 140 reacted with the antigen suspension refrigerated for 15 minutes and then allowed to stand 1 hour at room temperature, and 129 reacted with the antigen suspension refrigerated for 15 minutes. This is graphically illustrated in Figure 2.

When the sensitivity of the 27 to 28 hour antigen suspensions which failed to react 6 times (4%) were compared with the 15 minute refrigerated antigen suspension which failed to react 21 times (14%), the standard error of the difference was 3.25, and the difference in the two percentages was three times the standard error. Therefore, it could be concluded that the 28 hour antigen demonstrates statistically its greater sensitivity.

When the 27 to 28 hour antigen suspension and the antigen suspension refrigerated for 15 minutes plus 1 hour at room temperature which failed to react 10 times (6.7%) were compared, the standard error was 2.6. The difference was not 3 times the standard error; therefore, the difference in sensitivity is not statistically significant.

When the 27 to 28 hour and the 4 hour antigen suspensions were compared the standard error was 1.6. The difference was not 3 times the standard error, so that, although the indication was that the 4 hour antigen suspension was more sensitive yet statistically the difference is not quite significant. In a larger series this could probably be proved.

None of the sera failing to react with the other 3 antigen suspensions showed more than a doubtful reaction with the 4 hour antigen suspension.

Summary. After statistical analysis of the results, the following conclusions were drawn:

1. Mazzini antigen for routine use should be ripened 3 to 4 hours at room temperature.

2. Mazzini antigen which has stood at room temperature for 28 hours in the winter or even in summer heat up to 94° F. is more sensitive for emergency use than that ripened in the refrigerator for 15 minutes.

REFERENCES

1. Mazzini, L. Y.: Am. J. Clin. Path., 9, 163, 1939.
2. Preliminary Report on the Washington Serology Conference. Ven. Dis. Inf., 23, 161, 1942.

FURTHER EXPERIENCE WITH FURFURYL–TRIMETHYL–AMMONIUM IODIDE (FURMETHIDE) IN THE TREATMENT OF URINARY RETENTION DUE TO BLADDER ATONY*

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Some months ago, the treatment with furfuryl-trimethyl-ammonium iodide (Furmethide) of urinary retention due to bladder atony following surgery on the rectum was described.[5] It was concluded that this substance, a parasympathomimetic drug with strong action on the bladder, had certain advantages over such other drugs as mecholyl and doryl. Since that time, additional similar cases as well as instances of bladder atony due to a variety of other causes have been studied and treated under the described and modified régimes. The results have been striking enough to warrant publication of the data accumulated thus far. It was felt that these observations might be pertinent to the treatment of certain types of war casualties.

Material and Methods. Thirty-one patients have been studied. For purposes of discussion they have been divided into groups as follows: Group I. Patients who had operations at a distance from the bladder; Group II A. Patients who had operations with mild or moderate trauma to the bladder or its nerves; Group II B. Patients who had operations with severe trauma to the urinary bladder or its nerves; Group III. Patients with disease of the central nervous system.

In every case the volume of residual urine was measured immediately before the administration of the first dose of Furmethide and thereafter as indicated. Cystometric studies were also made. A number of the patients had previously received mecholyl or doryl in unsuccessful attempts to restore bladder function.

Observations. *Group I. Urinary retention in 8 patients following operations not involving the vicinity of the urinary bladder:* 2 patients after thyroidectomy, 2 patients after herniorrhaphy, 1 patient each after cholecystectomy, drainage of an abscess of the chest wall, ovariectomy and cecostomy. Six (75%) of the patients began to void normally after 1 or 2 doses of Furmethide subcutaneously. The 2 who did not void did sweat, salivate and/or lacrimate and had definite intensification of the desire to void.

Group II A. Urinary retention in 9 patients following slight or moderate trauma to the bladder or its nerves: 2 patients after delivery,

2 after hysterectomy, 2 after colporrhaphy, 1 after fracture of the pelvis, 1 after operation on a hernia which contained the bladder, and 1 after operation on an appendiceal abscess which extended into the pelvis. Seven patients (78%) responded favorably.

Case Studies. Case 57865 illustrates the course in a successfully treated case. B.W., a 28 year old woman, was operated on for appendiceal abscess extending deep into the pelvis. A drain was left in place after operation. The patient could not void and required catheterization for the first 5 days after operation. Furmethide was then started in doses of 4 or 5 mg. given subcutaneously (Fig. 1). Voiding began after the second injection, with volumes of residual urine of 150 to 900 cc. initially. The next day, however, the volume of residual urine was less than 1 ounce. After 10 days of subcutaneous and oral administration of Furmethide, the patient was able to void without medication; there was only a small volume of residual urine.
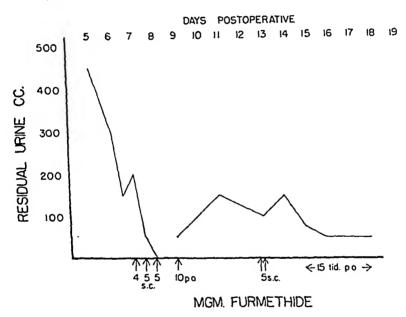
FIG. 1.—Case No. 57865.   Appendiceal abscess.

Case 58958 illustrates the course in an unsuccessfully treated instance and demonstrates the cause of failure in this case. R.T., a 52 year old woman with a history of diabetes, was operated on for rectocele and cervical erosion. She could not void after operation and required catheterization. The administration of doryl had no effect on bladder function. Cystometric studies on the 6th postoperative day revealed an atonic bladder. The administration of 3.5 mg. of Furmethide subcutaneously while the catheter was in place caused prompt contraction of the bladder. During the next 4 days, however, the drug in doses of 5 to 10 mg. given subcutaneously resulted in no voiding or only slight emptying of the bladder, in spite of the presence of other evidences of the action of Furmethide, such as sweating and salivation. Cystoscopy on the 13th postoperative day revealed marked bullous edema of the vesical neck which was considered to be acting mechanically to prevent emptying of the bladder.

Group II B.   Urinary retention in 6 patients following severe trauma to the bladder: after abdomino-perineal resections for carcinoma of the

rectum.   All of the 6 patients (including 3 previously reported[9]) responded favorably.   It is to be noted that none of the 6 patients responded favorably to the administration of Furmethide until after the pack was removed from the space formerly occupied by the rectum.
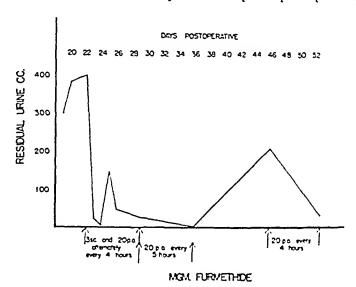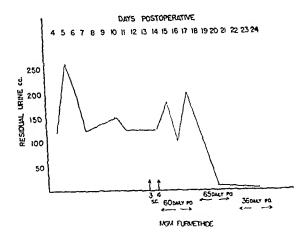
Fig. 2.—Case No. 65139.   Abdominal perineal operation.

Case 65139 (Fig. 2) illustrates the régime now in use in these patients. C.C., a 54 year old man, was unable to void after operation and was placed on constant drainage; his bladder was found to be infected. Constant drainage was discontinued on the 17th postoperative day, but the patient was still unable to void normally. Two days later he was given doryl, following which he voided 300 cc., leaving 300 cc. of residual urine. The next day the volume of residual was the same, after the voiding of 100 cc. following administration of doryl. Furmethide was started on the 22d postoperative day; the patient was given 3 mg. subcutaneously at 8 hour intervals and 20 mg. orally. Slight discomfort due to spasm of the bladder was noted on the first day, but not thereafter; moderate perspiration was the only persistent complaint. The volume of residual urine decreased rapidly. A week after the drug was started, the patient was discharged with orders to take 20 mg. by mouth at 8 A.M. and 1, 6 and 11 P.M. Seven days later the volume of residual urine was 0 cc. The drug was stopped for 10 days, after which the volume of residual urine was 210 cc. The drug was given again in doses of 15 mg. orally 4 times a day; at the end of a week the residual urine measured 50 cc. Increasing the dose to 20 mg. by mouth 4 times daily caused a slight decrease in the residual urine volume to 30 cc. He still required the drug 54 days after operation.

Group III.   Urinary retention in 8 patients with disease of the central nervous system: two instances of multiple sclerosis and one each of spina bifida, diabetic neuropathy, hydrocephalus, transverse myelitis due to metastatic carcinoma, vesical paralysis following operation for ruptured disk with spinal fusion at L5, and prolonged vesical paralysis following sympathectomy for hypertension. Seven of the 8 responded favorably.

Case 58720 (Fig. 3) illustrates the favorable action of the drug.   M.E., a 45 year old woman, was found to have multiple sclerosis 12 years before admission to the hospital.   Several months before admission for the treatment of uterine fibroids, urgency and frequency of urination, with the voiding of small volumes of urine, were noted.   Supravaginal hysterectomy shortly after admission was followed by cessation of voiding, and constant drainage was instituted. Two weeks later cystometric study (Fig. 3) showed a pressure curve characteristic of the neurogenic bladder; the administration of Furmethide resulted in a normal cystometric curve.   The volume of residual urine was 120 to 260 cc. before Furmethide was given.   Administration of the drug in doses of 20 mg.
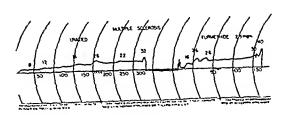
Fig. 3.—Case No. 58720.   Multiple sclerosis.

3 times daily caused a decrease in the volume of residual urine to 30 cc. Reduction in the dose of 12 mg. 3 times daily was not followed by an increase in the volume of residual urine.

Case 57631 illustrates the unfavorable action of the drug.   D.F., a 44 year old man, entered complaining of diarrhea, weakness of the legs and difficulty in voiding, the last progressing to complete retention a month before entry. Physical examination revealed absent knee, ankle and abdominal reflexes, atrophy of the leg muscles and poor tone to the rectal sphincter.   The urine was full of pus.   The spinal fluid contained 70 to 162 mg. per 100 cc. of protein as well as 0 to 5 lymphocytes per cmm.   Constant drainage was instituted and sulfathiazole given; the urinary infection soon subsided.   Cystometric studies revealed curves typical of the neurogenic bladder.   The curves returned to normal after the administration of 3.5 mg. of Furmethide subcutaneously, desire to void occurring when the bladder contained 75 cc. of urine.   Rectal and urinary incontinence became a complaint.   The administration of Furmethide thereafter caused a reduction in the volume of residual urine, but aggravated the urinary incontinence.   The rectal incontinence was not influenced.

Discussion. Furmethide (furfuryl-trimethyl-ammonium iodide) is related chemically to the other parasympathomimetic substances (Fig. 4). Several studies of its action in animals and in man are available.[2-6] Within a few minutes after the injection subcutaneously of

Fig. 4.—Chemical structure of Furmethide.

3 mg. or more in man, a diffuse flush, tachycardia, perspiration and salivation occur, varying in degree with the dose given. Simultaneously a desire to void is noted by the subject; cystometric evidence of increased vesical tonus[1] and roentgenographic evidence of contraction of the ureters and bladder[1] may be detected. With larger doses, transitory small decreases in blood pressure may occur; heart block has not been detected with the doses used.[2] The venous pressure is usually slightly elevated.[2] Visual accommodation occasionally may be disturbed.[2] Doses as large as 10 mg. given subcutaneously only rarely cause gastro-intestinal symptoms; fluoroscopic and roentgenographic studies have revealed no change in the motility of the stomach, colon and gall bladder.[2] Uterotubograms show no evidence of contraction of the uterine or tubal musculature.[2] The administration by mouth of as

much as 30 mg. causes only sweating and an increase in vesical tonus. Compared to other commonly used parasympathomimetic drugs, Furmethide has relatively less action on the bronchi and cardio-vascular system than mecholyl and on the gastro-intestinal tract than doryl and prostigmine. Its action on the urinary tract is much stronger than any of those drugs.

These pharmacologic studies in man strongly suggest that Furmethide is a useful drug in the treatment of the paralyzed bladder. Its striking effectiveness in the patients of Groups II and III above, in whom severe damage to the nerves innervating the bladder existed, is in harmony with this concept. It is also of interest that Furmethide was demonstrably effective in patients in whom doryl and mecholyl had previously been used unsuccessfully. The reason for its clinical effectiveness in the patients with bladder paralysis following operations distant from the bladder or with little trauma to the bladder, i. e., Group I and some of Group II A, is difficult to determine. It is probable that in some of these patients, particularly those in Group I, normal bladder function would have returned spontaneously in one or a few days. Anesthesia (including spinal anesthesia), medication (including morphia and atropine) and abdominal pain may have been responsible for the urinary retention observed in these patients. The use of Furmethide in these instances merely served to initiate vesical contraction, following which the bladder resumed its normal function. Its action under these circumstances is useful in that it may obviate the need for catheterization.

Although the cases here reported illustrate the necessity for individual analysis, certain general rules may be formulated for the use of Furmethide. Patients with acute vesical retention of unknown etiology, occurring during infectious diseases or in the postpartum or post-operative state (Group I), are easiest to treat. Regardless of the nature of the factors responsible for the failure to void, if the bladder can be stimulated by a parasympathomimetic drug (Mecholyl, Doryl or Furmethide), the proper reflex pattern may be reëstablished and spontaneous voiding instituted. Furmethide will accomplish this purpose in such instances with fewer doses and greater percentage of certainty if the bladder is not allowed to become overdistended. As soon as it is ascertained or suspected that such a condition exists, and it is known that no obstruction is present, a dose of 3 mg. of Furmethide may be administered subcutaneously. Partial or complete evacuation of the bladder should take place within 5 to 10 minutes; if this dose is ineffective, the dose should be increased by increments of 1 mg. until 5 mg. is reached. If the patient does not void, or if it is felt that only partial evacuation has occurred, it is to be considered that the drug has failed to work and, accordingly, catheterization must be instituted.

Patients who have reversible organic damage to the bladder, its parasympathetic peripheral nerves or the central nervous system itself, require a different type of régime. Inability to void completely or at all in the absence of obstruction to bladder outflow and large volumes of

residual urine are characteristic of this group. Cystometric observation is helpful, but actually not required, preliminary to starting therapy. The immediate postoperative state is no contraindication to its use, although the reduction in efficiency of any therapeutic procedure should be anticipated in the first few hours postoperatively. The initial dose is 2 mg. in children and 3 mg. in adults; it should cause voiding within 5 minutes. If neither voiding nor sweating occurs, the dose is to be considered inadequate. Under such circumstances, the patient is catheterized and an increased dose is given in 8 hours or at desire to void, the dose being successively 4, 5 and 7.5 mg. If 7.5 mg. do not cause voiding of any urine, however little, the drug need not be used further. If voiding occurs, the patient should be catheterized for estimation of the volume of residual urine, and the drug given every 8 hours daily. Oral administration of the drug contemporaneously with giving it subcutaneously is more effective than the latter alone. A 10 mg. dose of Furmethide should be given orally 2 to 3 hours after each subcutaneous dose and should be increased by 5 mg. each dose until sweating is produced in 1 to 2 hours after a given dose. This dose is then continued indefinitely. The volume of residual urine after voiding following subcutaneous administration of Furmethide is the index of improvement of bladder tone and accordingly it should be measured at least once daily. Reduction of the volume of residual urine to less than 1 ounce usually requires 1 to 5 days. Once the volume of residual urine is 1 ounce or less, the question of continuation of the above régime is dependent on whether the underlying process is cured or not. In the usual patient with bladder atony following hysterectomy, therapy is needed for less than 10 days; after abdomino-perineal resection of the colon and rectum for at least 4 weeks and sometimes indefinitely; and in such diseases as multiple sclerosis, indefinitely, or until remission occurs. In patients requiring prolonged administration of medication, it has been found possible after a time to use the drug orally only. If the combined type of treatment has been used previously in a given case, the effective oral dose for that individual, varying from 10 to 30 mg., is already established. If not, a few days of combined therapy is preferred to a complete transition from subcutaneous to oral medication. The drug, when given orally, may be administered 4 times a day (e. g., 8 A.M., 1, 6 and 11 P.M.). A slight rise in the volume of residual urine may occasionally be anticipated incident to the change. If recovery of bladder tone has not proceeded far enough at the time of the change to oral therapy, uncomfortable sweating may be produced in spite of which the volume of residual urine may rise over that found during the period of subcutaneous administration; reversion to the latter for a longer period may be necessary. It is unnecessary to emphasize that the smallest dose, subcutaneous or oral, which will produce the required effect upon the bladder is to be used, once a given routine is established.

In patients with severe, permanent damage to the peripheral or central nervous control of the bladder, the drug must be given indefinitely. Cases of transverse myelitis, such as occur in wartime, follow

this group, The anticipation of the necessity for indefinite use of large doses and the combined routes of administration, together with Credé manipulation of the bladder, are necessary in addition to the general approach outlined above.

The only side-reactions which thus far have proved troublesome have been perspiration and to a lesser extent salivation and lacrimation; vomiting occurred in one instance. These side-reactions are annoying, but not dangerous. After subcutaneous administration of the drug, sweating is more likely to be annoying than after oral medication. The body temperature may fall following profuse perspiration; the patient should be well covered at this time. In every patient studied, an amount of drug large enough to be effective, but too small to cause more than minimal discomfort has been found. The patients who experienced mild sweating consequent on taking the drug preferred it to the constant urinary drainage or repeated catheterizations which discontinuing Furmethide would mean.

· The drug may possibly be contraindicated in patients with ulcer or bronchial asthma; our observations permit of no conclusions in this regard. It does not appear to be contraindicated in the doses suggested in hypertensives or in patients who have arteriosclerosis but no clinical evidence of heart disease; it may possibly act deleteriously in patients with overt cardiac disease. It has no untoward effects in patients with thyrotoxicosis. Furmethide cannot be expected to relieve urinary retention due to vesicle neck obstruction caused by caruncles, enlarged prostates, neurogenic spasm, post-traumatic edema, or a large pack placed in the space formed during an abdomino-perineal resection; its use is contraindicated in such instances. Severe bladder infection predisposes to spasm and its occurrence requires a preliminary period of perhaps 10 days during which tidal or constant drainage, as well as chemotherapy should be employed. Patients who have incontinence as well as atony of the bladder are usually made more uncomfortable by Furmethide.

Summary and Conclusions. 1. Furmethide (furfuryl-trimethyl-ammonium iodide), a parasympathomimetic substance with strong action on the bladder, has been used in the treatment of bladder atony caused by a variety of factors in 31 patients.

2. Urinary retention was relieved in most patients; the volume of residual urine in such instances was markedly reduced.

3. Side reactions, consisting of perspiration and salivation, were occasionally troublesome but never dangerous with the doses used.

4. Obstruction of the vesical neck constitutes a contraindication for the use of Furmethide.

REFERENCES

1. Beaser, S. B.: Unpublished observations.
2. Bondy, P. K., and Altschule, M. D.: Am. J. Med. Sci., 204, 334, 1942.
3. Fellows, E. J., and Livingston, A. E.: J. Pharm. and Exper. Ther., 68, 23, 1940.
4. Fellows, E. J., and Livingston, A. E.: J. Pharm. and Exper. Ther., 71, 187, 1941.
5. Lifton, J. H., Beaser, S. B., and Altschule, M. D.: New England J. Med., 226, 138, 1942.
6. Myerson, A., Rinkel, M., Loman, J., and Dameshek, W.: J. Pharm. and Exper. Ther., 68, 476, 1940.

THE RAPID REMOVAL OF EXCESS JOINT FLUID BY ACID SALTS

EXPERIMENTS WITH TRAUMATIC HYDRARTHROSIS OF THE KNEE JOINT

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EFFUSIONS in the knee joint due to trauma are met constantly in the average general and industrial practice. The visible response to these traumata is not always an indication of their severity, as the synovial membrane may produce an enormous amount of effusion after some minor injury, or on the other hand very little fluid following a severe cartilage tear. Most of the knee injuries which result in more or less massive effusions consist of ligamentous sprains without demonstrable gross tearing or cartilage injury.[5] In any individual case, it is of course important to rule out by Roentgen ray any possibility of an intra-articular knee fracture.

For the past year experiments were under way to see if it was possible to reduce the amount of joint fluid in these cases of traumatic hydrarthrosis by a low salt, acid-producing diet, and by giving adequate dosage of ammonium chloride, in a similar manner to the removal of other forms of obvious or occult edema fluid. Of the 7 cases to be described, 1 was treated by salicylates, Ace bandage compression and short-wave therapy; another patient could not take ammonium chloride because it induced abdominal cramps; another had to be tapped on 3 occasions; and the others benefited in a rather marked way from the therapy to be discussed. This consisted of a low sodium chloride-acid forming diet, without restriction of fluids, and ammonium chloride in daily doses of 90 gr. (6 gm.), bed rest, and application of an ice cap to the involved knee. The last 3 cases can be used as controls, as they did not have the prescribed régime. Recently also, it was demonstrated that it was possible to increase or decrease the joint fluid in certain cases of rheumatoid arthritis by giving the patient adequate amount of bicarbonate of soda or alternatively ammonium chloride.[2]

Anatomy. The pertinent anatomy of the knee joint can be briefly summarized. There are two cruciate ligaments preventing forward and backward displacement of the knee joint. However, the muscles surrounding the joint, i. e., the quadriceps and its tendon, the hamstrings and the gastrocnemius really insure stability of the knee joint.

Physiology. The synovial fluid has been the subject of much recent experimental work. Certain conclusions may be drawn from these researches.[3,7]

The synovial fluid has an exceedingly close connection with the blood stream. If glucose is taken by mouth it reaches the knee joint very rapidly. It has been shown experimentally that particulate matter can be removed from the synovial fluid by phagocytosis of leukocytes and macrophages. Absorption may take place through

the capillaries or through the lymphatics of the synovial membrane. Isotonic solutions are easily absorbed from the synovial capillaries. Heavier solutions are absorbed more slowly. The synovial membrane is divided into two portions: the villus type covering the folded areas, which has in villi synovial cells that are filled with mucin; and the non-villus type that covers the smoother areas. The synovial fluid is formed principally from lymph plasma from the capillaries of the synovial membrane, plus mucin from the synovial cells. Allison and Ghormley[1] summarized the subject well when they stated that the synovial membrane is derived from the mesenchyme, that it can regenerate, that it has the power of secreting a fluid mainly derived from the blood plasma, but modified by mucin, and that certain cells may be found in the synovial fluid which are for the most part phagocytes, and help in removing the particles from the joint.

Case Reports. CASE 1. F. C., female, age 45, salesgirl, fell and injured her left knee during a snowstorm. Soon after, the left knee measured 34.2 cm. and the right 32 cm. in circumference at the mid-patella level. There was marked limitation of motion. Bed rest and an ice cap was advised for 5 days, without any change in either the measurements or in the mobility of the knee. Then the patient was put on ammonium chloride, 6 gm. (90 gr.) daily in divided doses, and a low sodium, acid-ash diet. Fluids were not restricted. After the 3d day, the reduction in circumference of the injured knee was at the rate of approximately 0.5 cm. a day, so that by the end of 7 days, the involved knee was but 0.5 cm. larger than the normal knee. The range of motion at this time was complete, and the patient was allowed out of bed for short periods of time. Ace bandage compression was applied throughout this period. The patient was soon able to return to work.

CASE 2.—J. B., male, age 20, college athlete, injured his right knee in a basketball game. Although the knee began to swell immediately, he completed the game and went to classes the following day. That evening, examination revealed a tense, immobile right knee measuring 40.3 cm. in circumference at the mid-patella level, as against 36 cm. for the left (uninvolved) knee. The patient was put to bed and an ice cap was applied to the knee. After 2 days, in which the knee had not decreased in size or changed in mobility, an orthopedic consultation was arranged. Tapping was advised, and 90 cc. of xanthochromic fluid was obtained. A tight bandage was applied and a posterior moulded splint. Within 12 hours the fluid had reaccumulated in the joint, the temperature had risen to 103° F., and the patient was hospitalized. Here the joint was tapped again and 150 cc. of bloody fluid was evacuated. A circular cast was applied for 2 weeks; the knee had shown no tendency to reaccumulate fluid at that time.

Six months after this event, the patient again injured his right knee by twisting it. As before, the part began to swell, but this time he went to bed. An ice bag was applied, but there appeared to be no results as far as diminution of the swelling in a 3 day period. Examination at this time revealed a tense, swollen, immobile right knee measuring 40.5 cm. in circumference; the left knee, 36 cm. The patient was put on a low sodium, acid-ash diet, and was given ammonium chloride, 6 gm. daily in divided doses. Fluids were not restricted. After the second day the size of the involved knee decreased, and the part became more mobile. One week later, the involved knee measured 36.6 cm. (a diminution of 3.9 cm.) and the mobility was normal. At this time the patient had to take his final term examination, and went to school in spite of medical objections. Compression by Ace bandage, was used while the patient was ambulant. There was no recurrence of the hydrarthrosis.

CASE 3. J. L., age 20, civilian Red Cross worker, twisted his left knee while playing soft-ball. The knee began to swell almost immediately. On

examination the left knee measured 39.5 cm. in circumference at the mid-patella level; the right knee, 36.5 cm. The involved knee was tense. The patient was immediately placed on a low sodium, acid-ash diet without limitation of fluids. Ammonium chloride was used in the amount of 6 gm. (90 gr.) daily in divided doses. There was remarkably prompt improvement, the knee becoming more mobile on the first day after therapy was started. At the end of 1 week, the involved knee had returned to normal (36.5 cm.) while the mobility had increased to almost normal range. Compression by means of an Ace bandage was applied and the subject was allowed to become ambulant.

Case 4. A. R., age 25, female, maid, injured her left knee by striking it against a table while at work. When first seen several hours later, the left knee measured 39.6 cm. in circumference, as against 36 cm. for the right (normal) knee. The patient was ordered to bed but refused, so that the treatment was largely ambulant. A low sodium, acid-ash diet was detailed and ammonium chloride tablets (90 gr.) a day in 4 divided doses was ordered. Fluids were not restricted. The swelling decreased rapidly while the mobility increased. At the end of 6 days the left knee measured 36.5 cm. (0.5 cm. more than the normal knee). Reëxamination at the end of 8 days revealed the left knee had returned to normal size (36 cm.). There was no return of the swelling.

Case 5 (Control). J. W., age 45, male, baker, hit his left knee against a machine with great force. The knee began to swell within several hours and the patient left the plant with great difficulty. On examination the left knee was markedly swollen, measuring 40 cm. in circumference at the mid-patella level; right knee, 37 cm. There was extreme difficulty in bending the knee. Paracentesis was advised but was refused, and therefore bed rest, salicylates, and an ice cap to the knee was prescribed for 5 days. During this time there was no decrease in the size of the involved knee. Short-wave therapy with a 12 meter portable machine was given every other day at the patient's home. At the end of 4 weeks, there was a decrease of 1.5 cm. in the circumference of the left knee, and the movement was improved. At this time the patient was allowed out of bed with Ace bandage compression to the knee and the short-wave therapy was continued. At the end of 8 weeks the left knee still measured 38.5 cm. in circumference (1.5 cm. more than the other knee) although movement was adequate, and the patient had therefore returned to work.

Case 6 (Control). M. B., female, age 40, chambermaid, fell down several stairs striking her left knee. She continued working even though her knee began to swell and continued to swell. The patient refused to stop work and was ambulatory throughout her course of therapy. Examination revealed that her left knee measured 37.2 cm. at the mid-patella level; right knee, 33 cm. A low salt-acid ash diet and ammonium chloride was presented, but could not be continued because of severe abdominal cramps. Short-wave treatment and Ace bandage compression was used throughout the treatment. At the end of 4 weeks of care, flexion and extension were still difficult, but were improved over the original state. The measurement was 36.5 cm. for the left knee at the mid-patella level, a diminution of 0.7 cm. At the end of 7 weeks, the left knee was considerably more mobile, although its circumference was 35.5 cm., 2.5 cm. more than the uninvolved knee. At this point contact was lost as the patient went to California.

Case 8 (Control). J. K., age 40, male, paperhanger, injured his right knee when he struck it against a wall. When seen 2 days after and, the right knee measured 40.2 cm. in circumference, left knee, 37 cm. Paracentesis yielded 95 cc. of a xanthochromic fluid. The measurement followed this was 37.5 cm. for the right knee. An Ace bandage was applied for compression. Four days later, the fluid had reaccumulated, and the involved knee measured 40.8 cm. Again tapping was resorted to, with the removal of 85 cc. of joint fluid. The measurement following this procedure was 38 cm. However, 3 days the joint fluid again reaccumulated measurement being 39.... The day after tapping a snug plaster cast was applied to the right joint. After ...

removal in 10 days, there was but slight reaccumulation (measurement 38 cm., *i. e.*, 1 cm. more than the uninvolved knee). Thereafter an Ace bandage was applied, and short-wave therapy was given every other day. Ten days later (*i. e.*, 29 days after the injury) both knees measured 37 cm. in circumference and treatment was stopped.

Comment. The diagnosis of traumatic hydrarthrosis (traumatic synovitis) of the knee with effusion is relatively easy. A direct or indirect injury to the knee, occasionally even a moderate twist, may cause a profuse outpouring of synovial fluid, and therefore a great swelling of the joint. This occurs without a cartilage tear or interarticular fracture, although these conditions must be carefully excluded before assuming that the more benign state exists. The synovial fluid in a traumatized joint is said to contain large numbers of erythrocytes, a variable white cell count, an increased amount of bilirubin (due to red blood cell hemolysis), and mucin. The icteric index of synovial fluid in traumatic effusions is usually above 5; on the other hand in the effusion of inflammatory arthritis the icteric index is below 5. The only other conditions causing increased bilirubin content of the synovial fluid consists of the hemarthrosis of hemophilia, sarcoma, xanthoma and tabetic arthropathy.[2]

The treatment of hydrarthrosis as usually carried out consists of an aspiration of the excess joint fluid, with the application of a tight adhesive plaster or plaster-of-Paris bandage, and rest for a period of several weeks. Not infrequently the fluid has a tendency to recur. The necessity of careful paracentesis must be stressed. Carelessness may result in the serious complication of suppurative arthritis, or as happened in one of the cases described, a hemarthrosis. Titus[9] treated an unusually large number of these cases with the static electric current, and he claimed a marked diminution of the extravasated fluid following several treatments. I have no familiarity with this form of treatment.

The effect of injested alkali on the content of joint fluid has been the subject of a recent communication.[3] The authors were able to increase the joint fluid in a case of rheumatoid arthritis by feeding sodium bicarbonate and to decrease the fluid by a low sodium diet and ammonium chloride in full doses. In our study of traumatic hydrarthrosis, strict attention was paid to the diet (see Table 1) which should be of low sodium content and preferably contain acid forming foods or, at least, be so selected that the combustion of foods would release as much acid as base. Salt in any form is interdicted. Fluids are not restricted. The rationale of this method of edema fluid removal was first enunciated by Newburgh,[4] but has recently been so clearly and succinctly stated by Schemm[8] that it bears repetition (almost but not exactly *verbatim*).

Edema fluid is a simple increase of interstitial fluid, and it can accumulate only if the materials that it holds in solution have been retained. For each 2 pounds of edema fluid, these consist of 10 gm. of an alkaline mixture of sodium salts (5 parts of sodium chloride and 1 part of sodium bicarbonate), and 1000 cc. of water as a solvent for

these salts. This alkaline edema fluid remains indefinitely, unless the bicarbonate fraction of sodium salts is used up by the acids formed from metabolism or by the injection of acid substances. Acidification causes the kidney to overcome this threat to the pH of the body fluid by elimination of the neutral or acid salts, or as it is usually expressed: acidification mobilizes the sodium of the body. As the sodium leaves the body by way of the kidneys, its water of solution is free either to leave the body as urine water, which causes weight loss and diuresis; or to leave the body as water vapor, thereby causing

TABLE 1.—AN ILLUSTRATIVE DIET LIST[9]

Breakfast

Fruit: Prunes, stewed figs, plums, other fruits only sparingly.
Cereal: Oatmeal, puffed rice or shredded wheat or farina with cream.
Eggs: Eggs., any style.
Breads: White toast or muffins or French toast.
Beverage: Coffee, or tea with cream.

Lunch

Fruit: Prunes (plain or juice) or cranberry sauce.
Meat or Fish: Choice of: beef, chicken, liver, mutton, pork, rabbit, veal; cod, haddock, halibut.
Vegetables: Corn or lentils (other vegetables must be used sparingly with the diet).
Salads: Prune and cottage cheese salad.
Breads: White bread or white flour muffins.
Beverage: Coffee or tea with cream.
Dessert: Nuts may be eaten as often as desired.

Dinner

Soup: Meat stock soup, preferably without vegetables. (They may be used in moderation only.)
Meat: Choice of meats or fish (as above in *Lunch*).
Eggs: Eggs, any style, may be substituted in the meal.
Vegetables: May be taken in small amount but should be buttered. Corn or lentils may be taken as often as desired. Peas and onions should be eaten less often. Spaghetti and macaroni are especially good.
Cheese: Cottage cheese salad, cheese in all forms are desirable.
Beverage: Coffee or tea with cream or sugar.
Dessert: Cranberries, plums and prunes are the only fruits allowed in limited amounts.

NO SALT TO BE USED IN COOKING OR AT THE TABLE

(6 gm.) per day) in the removal of the effusion in traumatic hydrarthrosis is worth reporting. The reasons given for not restricting fluid, paradoxical as it may sound, are good and sufficient. It cannot be claimed that a new treatment exists for the removal of effusions in the joints on the basis of the few cases described. Rather it is interesting from an experimental viewpoint, and substantiates fully the report of Jacobson, Leichtentritt and Lyons[3] in their attempt to influence the volume of joint fluid in rheumatoid arthritis.

REFERENCES

1. ALLISON, N., and GHORMLEY, R. K.: Diagnosis in Joint Disease, New York, William Wood & Co., p. 2, 1932.
2. COMROE, B. I.: Arthritis and Allied Conditions, Philadelphia, Lea & Febiger, p. 544, 1941.
3. JACOBSON, S. D., LEICHTENTRITT, B., and LYONS, R. H.: Am. J. Med. Sci., 204, 540, 1942.
4. NEWBURGH, L. H., and MacKINNON, F.: The Practice of Dietetics, New York, The Macmillan Company, p. 258, 1934.
5. PARNALL, E.: Journal-Lancet, 62, 90, 1942.
6. PELNER, LOUIS: The Diet Therapy of Disease, New York, Personal Diet Service (in press).
7. PEMBERTON, R.: Arthritis and Rheumatoid Conditions, Philadelphia, Lea & Febiger, p. 118, 1929.
8. SCHEMM, F. R.: Ann. Int. Med., 17, 952, 1942.
9. TITUS, N. E.: Arch. Phys. Ther., 14, 285, 1933.

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THE EFFECT OF ERGOTAMINE TARTRATE AND NEOSYNEPHRIN HCl ON THE WORK CAPACITY OF HUMAN MUSCLE*

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ONE of the minor complications of ergotamine tartrate therapy of migraine headache is the occurrence of occasional muscle cramps and weakness. O'Sullivan[5] states, "Thirty-seven (out of 97) of our patients complained of generalized weakness associated with the migraine attack. Fifteen individuals stated that after the alkaloid had eliminated the headache their legs felt tired and weak. It is rather difficult to determine whether this asthenia was caused by the drug or whether it was a coextent migraine phenomenon that the drug was unable to eliminate. A few of the patients state with certainty that this 'all in'

feeling is more noticeable to them after the drug than before." This weakness was sufficient in one of her patients to cause a serious fall. The purpose of our study was to determine, if possible, whether therapeutic doses of ergotamine tartrate would consistently produce muscle weakness in normal individuals. Experiments on neosynephrin HCl were also performed as a control to the subjective and blood pressure effect of the ergotamine tartrate.

Method. The Maison ergograph[2] was used to the point of fatigue to measure the work capacity. With this ergograph the extensor digitorum communis of either arm may be worked at a constant stroke rate and with a measured, uniform stroke. It has the advantages that no other muscles can be used to apply force to the work, the initial application of the hand is uniform because of the easily found landmarks, and the extensor digitorum muscle is otherwise little used in everyday life. The muscles were voluntarily contracted once each second, lifting a load sufficient to produce fatigue in 2 to 4 minutes. When, as a result of training, the subject could lift a given load for 10 full minutes, an increased load was applied in order to return the subject to the experimental range. As a training and stabilizing influence, the subjects exercised each arm daily for a fixed period of 10 minutes with a light load.

Ten thoroughly trained subjects were used after a training period which varied from 3 to 14 months, during which time the muscles of each arm were worked to fatigue 6 days a week. The load was increased by 300 gm. when a given subject was able to carry the previous load in steady state (10 minutes). Since the subjects frequently had greater variation in work output when working with an "easy" load, they were drug tested whenever possible 1 or 2 weeks after starting a new and heavier load. The 10 subjects used were male medical students and the authors. Two of these subjects had occasional periodic migraine headaches.

The recipients were not aware of the nature of the injected drug, and hence, placebo injections could be interspersed according to a prearranged schedule. The injection was usually made at 11 A.M. after a light breakfast. The work ability was tested at the height of drug action 90 minutes after the intramuscular injection of $\frac{1}{4}$ to $\frac{3}{4}$ mg. doses of ergotamine tartrate, or 15 to 30 minutes after 4 to 10 mg. intramuscular doses of neosynephrin HCl. The subjects were assigned to work either 30 or 90 minutes after the placebo injections of hypotonic saline. The subjects were seldom used oftener than once a week.

The data were graphed as deviations from the mean in fractions of the standard deviation calculated by using the 5 or more previous work periods and an equal number of subsequent work periods as the control period. The work outputs in kg./cm. of the left and right hands were first averaged and the standard deviation of these 10 or more data determined. The deviation from the mean of the averaged left and right hand work output on the experimental days was then compared to the standard deviation and expressed as a fraction or multiple of this deviation. By this method of calculation the gradual increase in work output which occurs in all training subjects was given equal weight both before and after the test day, and the calculation minimized the danger of recording any chance increased work output as a drug effect. While in the usual statistical treatment of biologic data any increase or decrease in work output beyond two standard deviations can be considered significant, in our treatment of the data we are comparing a single determination with a mean. Hence, this 2 S.D. rule can be applied only to the final mean for each drug.

Results. The data are summarized in the scatter graph, Figure 1. In general, no significant decrease in work output occurred after the intramuscular injection of ergotamine tartrate. The 3 decreases

greater than 2 S.D. did not occur twice in the same individual, for each of these subjects was given 2 injections of ergotamine tartrate. The mean of the work output in 21 trials on the 10 subjects was —.55 standard deviations (S.E. of mean = .26), which was less than the mean for either the placebo injections or the neosynephrin HCl injections. The work capacity after the placebo injections varied from one negative standard deviation to 1.9 standard deviation plus. The mean for the 15 trials was +0.36 standard deviation (S.E. of mean = .25). This slight increase must be attributed to the psychic effect of the injection. In the case of neosynephrin HCl the work output after intramuscular injection of 5 to 10 mg. was marked in 2 instances and above 2 S.D. in 6 out of 20 trials. The mean increase was also
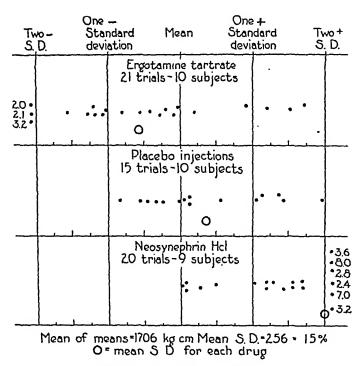
Fig. 1.—Scatter graph of work output of the 10 trained subjects. The work output on the test day is graphed as a fraction of the S.D. determined by analysis of the preceding and subsequent data. One mean S.D. is equal to 256 kg./cm. or a 15% change in work output.

significant, being 2.04 standard deviations (S.E. of mean = 0.15). Two of the subjects had periodic migraine headaches, and the mean of their calculated work output after ergotamine tartrate was —1.47 standard deviation. However, their average effort with the placebo injection was —.29 standard deviation and only +.05 with the neosynephrin HCl injection. Thus, they were relatively low in all experimental drug trials of work output.

Subjective symptoms from ergotamine tartrate were surprisingly few even with doses of ⅔ mg. The subjects reported slight nausea, masseter trismus, slight dizziness, and occasional sweating. No vomiting occurred. The 2 migraine subjects noted that the subjective effect of ergotamine tartrate was much less than those symptoms elicited

by an equal dose of the drug at the time of a headache. Occasional symptoms elicited by neosynephrin HCl were pilomotor activity and frontal headache of short duration. The maximum slowing of pulse rate occurred 30 minutes after neosynephrin HCl, and this was taken to be the time of maximum drug action.

Discussion. By far the most significant finding of this study was the increased work capacity after the intramuscular injection of neosynephrin HCl. Since this drug is sympathicomimetic and chemically similar to epinephrin, one might, according to the emergency theory of epinephrin action, expect an increase in work output. However, a search of the literature has failed to reveal any exact studies of the work capacity in trained subjects after epinephrin injections. These data must, hence, stand without comparison to epinephrin data.

The effect of an injection of any kind has always been given a high psychic value by cautious experimenters when the data have not been or cannot be subjected to statistical analysis. The findings in this study that injection of a placebo results in only a $+.36$ S.D. mean rise in work output speak for the intense endeavor and stability of our subjects. The data also indicate that in normal subjects, at least, the psychic effect of a simple injection has been hitherto overrated.

Finally, when the effect of the smooth muscle stimulant, ergotamine tartrate, is compared with the smooth muscle stimulant, neosynephrin HCl, the failure to obtain an increase in work output with ergotamine tartrate may be significant, since they were used in doses which produce proportionate rises in blood pressure.[1,4] By this comparison the ergotamine tartrate effect to slightly decrease work capacity assumes possible significance. However, the only definite conclusion to be drawn at present must be that muscle weakness occasionally encountered clinically in treated migraine patients cannot be due to the direct action of ergotamine tartrate. Some predisposing factor in the migraine syndrome must potentiate the slight effect of ergotamine tartrate on striated muscle.

Summary. The work capacity of a group of trained subjects was:

1. Decreased (but probably not significantly so) by intramuscular ergotamine tartrate.

2. Slightly increased by intramuscular placebo injections.

3. Significantly increased by intramuscular neosynephrin HCl injections. The muscle weakness occasionally reported from ergotamine tartrate of migraine headache cannot be due entirely to the drug. Some predisposing migraine factor must be involved.

REFERENCES

1. Brock, S., O'Sullivan, M. E., and Young, D.: Am. J. Med. Sci., 188, 253, 1939.
2. Maison, G. L., and Brocker, A. C.: Am. J. Physiol., 132, 390, 1941.
3. O'Sullivan, M. E.: J. Am. Med. Assn., 107, 1208, 1936.
4. Pool, J. L., Von Storch, Th. S. C., and Lennox, W. G.: Arch. Int. Med., 57, 32, 1936.

CARDIAC ARREST BY THE ACTION OF POTASSIUM*

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The earliest report of potassium poisoning in nephritis is that by
W. G. Smillie in 1915 from the medical clinic of the Peter Bent Brigham
Hospital.[20]   He described a temporary episode of collapse with vomit-
ing, following the administration of 10 gm. of potassium chloride as a
diuretic.   The patient had been diagnosed as having chronic nephritis
with uremia.   Smillie approached the problem experimentally on the
basis of Reid Hunt's unpublished observation of the toxicity of orally
administered potassium salts for nephrectomized guinea pigs, and
found that 1 gm. of potassium chloride orally was quickly fatal to
rabbits with nephritis induced by uranium nitrate.

In view of more recent knowledge of the action of potassium it is
evident that the reaction of Smillie's patient illustrates an irritating
effect of this substance acting locally on the gastro-intestinal tract.[30]
At the same hospital new methods of investigation have since made
possible a demonstration of the toxic effect of accumulated potassium
ions in the body.

Toxic effects of potassium had been suspected previously in a variety
of conditions,[19,26] but there was no way of demonstrating whether or
not they had actually occurred.   The recent development of exact
micro-methods for the determination of serum potassium and the dis-
covery of a specific sequence of electrocardiographic changes accom-
panying progressive elevation of the serum potassium in dogs[31] has
made it possible to establish conclusively that in the first of the 2 cases
described here, cardiac arrest resulted from an elevation of the serum
potassium.

A search through the collection of electrocardiograms (ECG) of
Dr. S. A. Levine subsequently revealed a similar tracing.   This was
from a second patient who also demonstrates the characteristic ECG
and the final stages of the clinical course of potassium poisoning, al-
though no potassium determinations were made.

Case Studies.   Case 1.   Med. rec. No. 61888.   *Oliguria and azo-
temia, failure of adequate urinary potassium excretion, characteristic ECG
changes of potassium poisoning, and a terminal flaccid quadriplegia.*

C. C., a 39 year old married negro painter, entered the Peter Bent Brigham
Hospital on April 26, 1942, complaining of abdominal distress and nausea
accompanied by a diminishing output of urine.   He had been examined in the
dispensary 13 months before entry because of low back and leg pain following

an automobile accident. At this time the blood pressure was 160/110. The urine was normal microscopically and had a specific gravity of 1.022. The spinal fluid was normal. Four months prior to entry when he was examined for government employment, the blood pressure was 160/90. The job which he undertook in apparently good health consisted of repair work and painting in a shipyard, an occupation which was not new to him. He had first become an apprentice painter in 1915, at the age of 12.

A month after he had started work, he began to take time out for sickness. For 3 months he had general malaise and occasional vomiting. In the last 3 weeks there was also a mild recurrent peri-umbilical pain. The discomfort gradually increased up to the 5th day before admission. On that day there was return of the numbness in the left leg which had occurred at intervals since his automobile accident 19 months before. While at lunch on that day he experienced a severe exacerbation of the abdominal pain, accompanied by emesis and diarrhea. He also had a shaking chill with fever of 103° F. In the 4 days prior to admission no more bowel movements occurred, but vomiting and anorexia continued. At the same time the abdominal discomfort gradually improved. He described the urine as deep amber in color and amounting to only a pint a day for 4 days.

Physical Examination. The patient was a well-developed negro who appeared comfortable but complained of feeling tired. He had a temperature of 99° F. by mouth. The ophthalmoscopic examination revealed minimal arteriovenous nicking of the retinal vessels. His heart sounds were of good quality and regular with a soft systolic murmur at the apex. The heart rate was 90 per minute and the blood pressure was 165/95. The abdomen was somewhat tense and rounded, but there was no tenderness of the costovertebral angle and only slight peri-umbilical pain on deep pressure. He had no peripheral edema. The tendon reflexes of the extremities were present and equal bilaterally.

Laboratory Data. The blood Hinton and Wassermann reactions were negative. The hemoglobin concentration was 12.6 gm. per 100 cc. and the hematocrit 43%. The white cell count was 9500, with a normal differential. A special search revealed no basophilic stippling of the red cells. The blood urea nitrogen was 91 mg. per 100 cc. on the day of entry and gradually rose to 141 at the time of death. On the 3d hospital day the non-protein nitrogen of the serum was 137 mg. per 100 cc. The total serum protein at this time was 6.6 gm. per 100 cc., of which 4 gm. were albumin and 2.6 were globulin. The icteric index was 8. Serum collected 24 hours before death contained 8.85 m.eq./l.* of potassium, and a specimen obtained a few moments *after* death contained 10.50 m.eq./l. of potassium.

The urine was turbid, amber colored, and had a specific gravity ranging from 1.008 to 1.012. The albumin content was 3+ by the heat and acetic acid test, and there were many red cells and white cells in the centrifuged sediment. After standing with added HCl the urine developed a rosy tint, but contained no porphyrins. The 425 cc. excreted during the last two days of life contained 20.6 m.eq. of potassium per liter. A stool specimen obtained by enema appeared normal and contained no occult blood.

Hospital Course. During the 6 days in the hospital he was afebrile, but remained in bed feeling nauseated, anxious and weak. He had to be urged to eat, and there were repeated episodes of vomiting. Despite an intake of 13,870 cc. of fluid orally and by vein, which averaged nearly 3 liters a day for 5 days, the entire output of urine amounted to less than 2 liters of 300 cc. per day during this period. He was also continuously constipated.

A 5 A.M. on the 5th hospital day, 24 hours before death, he experienced difficulty in reaching for the bell cord to call for a urinal. Immediately thereafter he lost all power to move the extremities except for an occasional slight flexion of one or two digits. However he was able to void at this time and again on a subsequent occasion.

* Milliequivalents or millimols per liter. (To convert to milligrams per 100 cc., multiply by 3.9).

With the advent of paralysis he became frightened and anxious, but experienced no pain. The extremities became cold and wet, and the tendon reflexes could no longer be elicited. Yet there was no paralysis of the head or trunk muscles and his mental faculties remained clear. At one time there were slight twitches about the mouth and the jaw jerk was hyperactive. No sensory disturbances were observed at any time. A lumbar puncture revealed no abnormalities of the spinal fluid.

The paralysis was accompanied by transitory episodes of bradycardia, but the blood pressure remained high and the pulse quickly returned to the usual rate of about 80 per minute. The ECG 4 hours after the onset of paralysis (Fig. I A) showed absent P waves, widespread intraventricular block, regular rhythm and a rate of 63 per minute.

Toward the latter part of the day there was evidence of some degree of recovery. By evening he was able to move his arms freely, but there was still weakness. The left knee jerk returned temporarily. He also recovered some use of the thigh and calf muscles, and could wiggle his toes slightly. At 10:45 P.M. he received 4.5 gm. of potassium chloride by mouth, on the possibility that the paralysis might be akin to familial periodic paralysis and would respond similarly.

However, by 1 A.M. the paralysis was again worse. The heart sounds were regular, with the same systolic and a new diastolic murmur at the apex and a reduplication of the second sound in the pulmonic area. The ECG at this time showed an even wider spread of the ventricular complexes (Fig. I C) than was seen on the first record. The pulse repeatedly slowed momentarily from rates of 60 or 80 to 20 or 30 beats per minute. At 5:45 A.M., after a sleepless night, he felt fatigued but was conscious and well oriented. The pulse rate was 74 and the quadriplegia had returned.

During the last hour of life ECGs were recorded almost continuously. The cardiac rhythm remained regular until about 15 minutes before death (Fig. I B), when momentary pauses began to appear after every third and then after every second beat (Fig. II D, E, F). A few moments before death he became drowsy, asked to have the bedclothes pulled away and wanted to have his hands rubbed. They had become colder and wetter. His speech was thick, and he seemed increasingly apprehensive, yet even at this time voluntary elevation of the head from the pillow was accompanied by a strong contraction of the abdominal muscles.

On the ECG, lengthening periods of asystole (Fig. II G) were interrupted by intervals of acceleration of the pulse to the original rate of about 80 per minute. Transitory intervals of ventricular fibrillation (Fig. II H, I) were followed by increasing periods of asystole interrupted by varying abnormal beats (Fig. II J; Fig. III K, L, M). After a very long asystole at 6:45 A.M. (Fig. III N) he became cyanotic and respirations ceased except for a few sporadic efforts. Two intracardiac injections of 1 mg. of epinephrin in water were followed by fibrillation of the ventricle (Fig. III O) but no heart sounds were heard and no peripheral pulse was felt. Each time, after the injection of 1 gm. of magnesium sulfate in water, the fibrillation ceased and single efficient cardiac contractions occurred. Heart sounds could be heard and pulsations could be felt at the wrist, but this activity was infrequent and soon died out. Artificial respiration was administered, but at 7:10 A.M., 25 minutes after the cessation of spontaneous respiration, fibrillary motion of the heart ceased entirely and there was no further response to epinephrin.

Autopsy. There were 300 cc. of clear fluid in the right pleural cavity and 200 cc. in the peritoneal cavity.

The heart was noticeably dilated and weighed 470 gm. Microscopically, there were some tiny scattered areas of myocardial fibrosis and atrophy, in a few of which were fibroblasts, lymphocytes and rare erythrocytes. The blood-vessels were normal.

The abdominal viscera were engorged, the liver, which weighed 1580 gm., appeared normal except for prominence of the lobular markings. Microscopic examination revealed atrophy and loss of liver cells in the pericentral areas.

This was accompanied by small deposits of lipoid material and a number of mononuclear cells containing brownish pigment.

The kidneys were enlarged and weighed 310 and 380 gm. The capsules stripped easily. On cut sections the architecture was well preserved but there was some bulging of the parenchyma. The microscopic sections showed edema, a chronic type of cellular infiltration of the interstitial tissue and degenerative changes in the epithelium of the renal tubules with occasional evidence of regeneration. There was very little abnormality of the vessels or glomeruli.

In the brain there was flattening of the convolutions of the cortex, but otherwise nothing grossly or microscopically abnormal in it or the upper cervical cord. No significant changes were found in other organs.

Discussion. This patient does not exhibit the usual syndrome of uremia as seen in the terminal stages of chronic renal disease. The completeness of the renal failure is reflected in the water retention, the fixed specific gravity and the rapid increase in the blood urea nitrogen, and even more significantly in an almost complete retention of potassium. Except for the paralysis, the clinical course of this patient corresponds closely to the observation of the rapid onset of collapse and death in dogs dying of spontaneous potassium intoxication after bilateral ligation of the ureters.[10]

In spite of blood levels between 8.85 and 10.5 m.eq./l. there were only 0.32 gm. of potassium in the 425 cc. of urine excreted in the last 48 hours. Calculated on this basis, 0.23 gm. of potassium were excreted in 300 cc. of urine each day for the last 10 days of life. This rate of excretion with an average dietary intake of 3.4 gm. a day would have allowed a retention of approximately 30 gm., less a negligible loss of about 0.3 gm. a day[17] in the feces. Although it is probable that in the last few days the dietary intake of potassium was less than that in the average diet, the significance of the disturbance in balance remains evident.

Because of the similarity of the ECG records from this patient and those reported as resulting from experimental potassium intoxication in dogs, two samples of serum and one of urine were analyzed by the chlorplatinate method.[8]* Both serum specimens were collected with care in a dry syringe. The first was centrifuged immediately; the second after standing for a few hours at room temperature. Examined spectroscopically, both were free of hemoglobin. The urine was a sample from the 425 cc. excreted in the last 2 days of life.

Although the normal level of serum potassium is between 4 and 5 m.eq./l., in this patient it was 8.85 20 hours before death and 10.5 a few moments after death. This is an elevation capable of causing cardiac arrest in dogs.[31]

The ECG changes could not be attributed to the small foci in the microscopic sections of the myocardium. Myocardial lesions similar to these have been described in uremia and demonstrated in the rare cases in which there was no widespread vascular disease.[7] However, neither with uremia[34] nor with myocarditis from other causes are there ECG changes comparable to those resulting from potassium intoxication.

The demonstration of fatal potassium poisoning in this patient, as

* The analyses were made by Dr. A. W. Winkler of the Department of Medicine, Yale University School of Medicine.

in experimental animals, is based on clinical rather than anatomic evidence. No structural changes have been observed at postmortem in animals experimentally poisoned with potassium, and except for the dilatation of the heart, none of the pathologic findings in this patient should be attributed to the action of potassium. ✓

CASE 2. Med. rec. No. 20525. *Oliguria and azotemia, the characteristic ECG changes of potassium poisoning, and a terminal flaccid quadriplegia, following the therapeutic administration of large quantities of potassium salts.*

M. H., a single, 50 year old, white chauffeur entered the Peter Bent Brigham Hospital on February 15, 1923, complaining of inability to pass urine. He had used alcohol for years. Previous illness was denied.

Six days before admission, after 3 or 4 drinks of home brew, he appeared so "wild and unnatural" that a doctor was called, but no actual delirium tremens developed. He worked and felt well the following day and that night had another drink. The next morning he complained to his physician that he had passed no urine for 4 days. The administration of a proprietary diuretic and magnesium citrate had no effect. On the day before admission, after 5 days of anuria, catheterization yielded only a few drops of urine.

Physical Examination. He was a well nourished male who appeared comfortable and alert. Both the breath and the skin had a uriniferous odor. The skin appeared pasty, and there was a moderate edema of the lids and conjunctivæ. The optic fundi were normal. About the mouth there was a slight tremor during speech. The examination of the heart and lungs was not remarkable. The blood pressure was 175/98. The pulse rate was regular at 80 per minute. The abdomen was distended and diffusely tender. In the extremities the musculature was normal and the reflexes were described in detail as equal and active. There was no peripheral edema, and his general condition was good.

Laboratory Data. The erythrocyte count was 4,000,000 and the hemoglobin was read as 100% (Sahli). The leukocyte count was 9600, with a normal differential. The blood urea nitrogen rose from 105 mg. per 100 cc. on admission to 128 at death, while the blood creatinin increased from 17.1 mg. per 100 cc. to 19.1. The carbon dioxide-combining power of the plasma remained at 60 vol. %.

Four urine specimens were pale and cloudy, with specific gravities from 1.008 to 1.010. They contained a moderate amount of albumin and numerous red cells, white cells and casts. A stool on the 3d day contained mucus, but no occult blood.
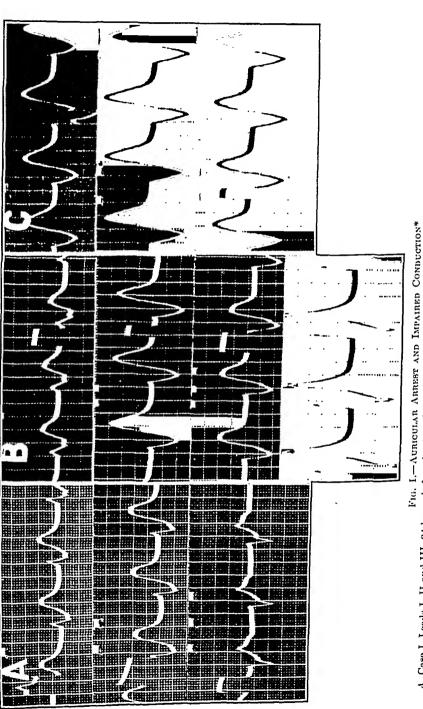
Twenty-four hour urine specimens were analyzed quantitatively on the 5 days before death. There was a progressive increase in urine volume from 55 cc. to 1 liter per day, associated with an increase in the total excretion of urea and total nitrogen, titratable acid, creatin and creatinin. However, the amounts excreted were never more than a small fraction of the normal minimal values for these substances. No potassium determinations were made on the blood or urine.

Hospital Course. The patient felt and appeared fairly well for 5 days but on the 6th day developed a flaccid quadriplegia and died. During his hospital stay he continued to have abdominal distention, puffiness about the face and a uriniferous odor. He remained afebrile. The blood pressure, pulse and respiration did not change appreciably. As the daily urine output increased his weight declined from 75 to 71 kg.
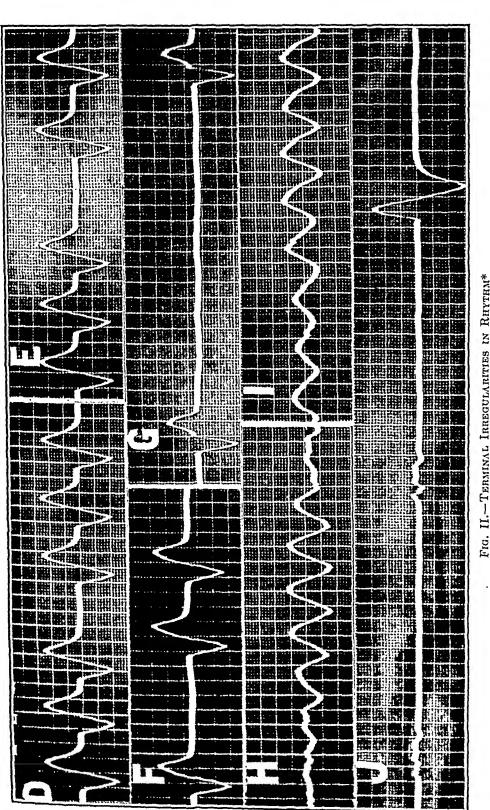
Because of the anuria he was given a course of therapy routinely used for mercury poisoning, apparently for diuretic effect as well as for the purpose of preventing acidosis. This was called the Lambert treatment and included the administration of almost 2 gm. of potassium bitartrate in 250 cc. of water every 2 hours. It also included the periodic administration of 4 gm. of potas-

FIG. 1.—AURICULAR ARREST AND IMPAIRED CONDUCTION*
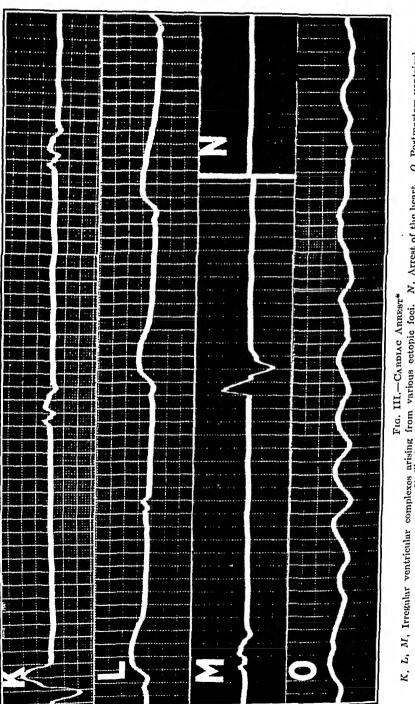
A, Case I, Leads I, II and III, 24 hours before death and 4 hours after the onset of paralysis. Rate: 63 per minute P waves absent. Widespread intraventricular block. QRST: 0.6 second. Elevated T waves. B, Leads I, II, III and IVF, 5 hours before death. Rate: 50 per minute. Further elevation of T wave. Increased voltage. C, Leads I, II and III, 30 minutes before death. Rate: 65 per minute. The ventricular complex has become as mooth biphasic curve.

* Reproduced at ⅔ original size.

FIG. II.—TERMINAL IRREGULARITIES IN RHYTHM*

D, E, F, Ventricular complexes in groups of 3 and then groups of 2, at increasing intervals. G, Bradycardia. Rate: 14 per minute. H, I, J, Transient intervals of slow ventricular fibrillation followed by resumption of single varying abnormal complexes at irregular intervals.

* Reproduced at ⅓ original size.

Fig. III.—Cardiac Arrest*

K, L, M, Irregular ventricular complexes arising from various ectopic foci. N, Arrest of the heart. O, Postmortem ventricular fibrillation after intracardiac injection of epinephrin.

* Reproduced at ⅓ original size.

sium acetate in 500 cc. of water, by Murphy drip, infused slowly per rectum. The potassium acetate was given once on the 2d hospital day, once every 4 hours on the 3d, and thereafter was reduced to 2 gm. in 500 cc. of water at 8 hour intervals. On this régime he continued to feel weak and suffered from recurrent nausea and vomiting.

On the morning of the 6th hospital day the patient complained of increasing weakness in the legs. At 10:30 A.M., 5 hours before death, he was unable to bend his knees and showed marked weakness of the arms. The respiration remained normal and his mental state was entirely clear. At 1:30 P.M. the pulse had slowed to 28 beats per minute. At 3:10 P.M. an ECG was taken which showed "extraordinary curves with defective intraventricular conduction, suggestive of cor mortuum" (Plate IV).

Immediately after this, while he was being placed on his side for a lumbar puncture, the pulse became very slow and irregular, with dropped beats, and then stopped. The respirations had remained normal, but ceased a few seconds later. The patient was rational and answered a question within 30 seconds of his death, which occurred at 3:25 P.M., 15 minutes after the ECG had been taken.
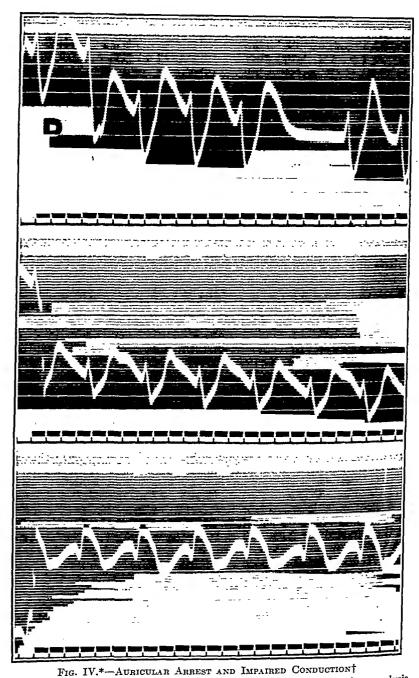
Autopsy. The postmortem examination was reported by Dr. G. B. Magrath, the medical examiner, as showing diffuse chronic and acute nephritis, dilatation of the heart and edema of the lungs and brain.

Discussion. This patient survived 5 days of anuria before entering the hospital. During the 6 days on potassium therapy, there was an increase in urine volume and evidence of a beginning return of renal function. However, this return of function was never sufficient to affect appreciably the progressive course of the azotemia. The total daily excretion of the substances studied remained so small that the renal failure even on the last day of life was still nearly complete. From the laboratory data and other features of the case it is now apparent that in spite of a beginning diuresis the intake of potassium salts exceeded his excretory capacity. The total amount administered included about 20 gm. of the bitartrate daily and 4 to 6 or more gm. a day of the citrate for the last 5 days of life.

The final sequence of events corresponded closely to that of the case previously described, but was more rapid. There was a transitory bradycardia 2 hours before death, but regular rhythm was maintained. There was no change in the blood pressure until the end. The ECG (Fig. IV) showed arrest of the auricles and widespread intraventricular block. Terminal irregularities of the pulse were observed, corresponding with those of the previous case immediately before cardiac arrest. In this instance, as in the first case and in the experimental animals, the heart beat ceased before the respirations and the heart stopped in diastole. Again it may be noted that the patient remained conscious and able to speak up to the moment of death. In this case the diagnosis of fatal potassium poisoning is established on the basis of the clinical course and the electrocardiogram.

The Electrocardiographic Diagnosis of Potassium Effect. The work of Winkler, Hoff and Smith has made possible an ECG diagnosis of potassium poisoning in man. They showed that in dogs a slow increase of the serum potassium from normal levels of 4 to 5 m.eq./l. to 14 or 16 was accompanied by a progressive elevation of the T waves, depression of the S-T segment, intraventricular block, loss of P waves, and finally

FIG. IV.*—AURICULAR ARREST AND IMPAIRED CONDUCTION†
Case II, Leads I, II and III, 15 minutes before death, and 4¾ hours after paralysis.
Rate: 85 per minute. Absent P waves. Widespread intraventricular block. QRST:
0.75 second. The T waves are elevated and overlap each succeeding complex.

* Standardization deflection = 3 millivolts.
† Reproduced at ⅔ original size.

cardiac arrest.   They also found that the ventricular fibrillation reported by earlier workers did not occur if the infusion of potassium salt was given slowly.[31]   A rapid administration resulted in ventricular fibrillation.[15] ✔

Subsequent studies demonstrated spontaneous potassium poisoning regularly in surgically anuric dogs[10] and occasionally in adrenalectomized dogs[32] as suggested by the work of Nicholson and Soffer.[16] Wood and Moe[33] found in heart-lung preparations from dogs that atrial and ventricular arrest occurred at average plasma potassium concentrations of 8.5 and 9.5 m.eq./l., respectively.

In man, the earlier effects of potassium on the heart have been described in the ECG of persons receiving potassium salts orally.   These reports have shown elevations of the T waves[24] and in some cases an increase also in the P–R interval.[25]   Two reports have also shown what now may be recognized as advanced toxic effects of potassium, including absent P waves and extensive intraventricular block.   Each record was taken a short time before death.   One of these was interpreted as showing a toxic effect resulting from the therapeutic administration of potassium salts, but no potassium determinations were made and cardiac arrest by potassium was not suggested.[21]   The other, from a patient in uremia, was interpreted as due to a toxic depression of the Purkinje system, but the nature of the toxin was not specified.[29]

In the 2 cases described here the ECG changes observed in association with poisoning of the human heart by potassium were as follows:

The rhythm remained regular most of the time.   The ventricular complexes increased in duration and developed progressively smoother and more rounded contours in contrast to the sharp QRS and T waves of the normal ECG.   In Case 2 the successive complexes were so prolonged that they overlapped each other.   In Case 1 the S–T segment was progressively depressed (Fig. I A, B) and then completely overlapped.   The T waves became more rounded and markedly elevated. The sequence of changes preceding cardiac arrest in Case 1 included increasingly frequent and prolonged pauses in the rhythm, brief runs of slow ventricular fibrillation, and a series of variously deformed ventricular complexes.   These changes were interpreted as indicating: (a) Suppression of auricular activity; (b) progressive slowing of conduction in the ventricles; (c) arrest of the heart associated with terminal irregularities of the rhythm and ectopic ventricular beats.

The absence of P waves results from arrest rather than from fibrillation of the auricles, as is shown by the persistence of regular rhythm. A degree of delay in conduction as great as that observed in these 2 cases is usually interpreted as representing bundle branch block. In these tracings, however, it represents an effect of potassium on the whole heart similar to that which occurs locally following direct topical application of potassium solutions to the mammalian heart.[27]

The runs of ventricular fibrillation which accompanied cardiac arrest in Case 1 correspond to the slow, reversible potassium fibrillation which occurs in association with dilatation of the heart.[15,28]   The postmortem ventricular fibrillation recorded was a non-specific effect from

intracardiac epinephrin injection rather than an effect of potassium. The increased irritability of the heart due to epinephrin together with the slowing of conduction by potassium provided an ideal condition for the development of circus movements.   Experimentally a rapid intravenous injection of potassium alone acts similarly.[15] The varying form of the terminal ventricular complexes represented varying sites of ectopic impulse formation in the ventricles.

The striking changes observed in the tracings from these patients provide a method for demonstrating physiologic effects of a quantitative disturbance in one of the plasma electrolytes. They also provide an etiologic explanation for certain bizarre terminal ECGs, formerly diagnosed non-specifically as *cor mortuum* or "dying heart."

Paralysis of the Extremities.   In experimental potassium poisoning no paralysis has been observed.   The animals die of cardiac arrest without accompanying evidence of paralysis.   However, a functional depression of nervous tissue and skeletal muscle has been demonstrated following the topical application of 25 m.eq. of potassium chloride per liter.[3]   In man, marked weakness of the extremities accompanied by paresthesia has followed an oral dose of 15 gm. of potassium chloride.[2]   Paresthesias after comparable doses have been reported, accompanied by marked elevation of the T waves[25] and a somewhat lower serum potassium than that of Case 1.[12]

In the hours preceding cardiac arrest, paralysis was a striking feature in the course of each of the 2 patients described here.   Since both were in uremia, substances other than potassium were also accumulating, although none of these are known to cause this type of paralysis.

The loss of motor power in each instance passed upward over the extremities in an ascending order.   In the first case it lasted for 24 hours with an interval of partial remission.   In the second it was present continuously for 5 hours.   In each it was preceded by a sense of weakness and heaviness of the limbs, but by no other paresthesia or demonstrable impairment of sensory function.   The musculature remained flaccid, and the tendon reflexes were absent.   The head and trunk were not involved and there was no interference with respiration or micturition.   There was no impairment of mental functions, although speech became thick just before death.

An apparent indication of a relationship of this condition to increased serum potassium is the fact that the subsiding paralysis in Case 1 returned after an oral dose of potassium chloride.   Whether or not such was the case, the occurrence of sudden flaccid paralysis in association with high serum potassium suggests that it is important to differentiate such episodes from an attack of familial periodic paralysis.

The low serum potassium which occurs in familial periodic paralysis is associated with ECG changes unlike those described in these 2 cases. The changes in familial periodic paralysis include bradycardia, moderate block in conduction, and a characteristic flattening of the T waves.[22,23]   These changes disappear after the injection of atropine,[23] while those from high potassium do not.[31]   Moreover, once it is appre-

ciated that such an attack may occur in association with an elevation as well as with a diminution of the serum potassium, the differential diagnosis need present no difficulty, since high serum potassium is unlikely in the absence of advanced renal failure or anuria.

Effect of Renal Failure on the Serum Potassium. Normally the serum potassium level is controlled by the kidney, and any excess is promptly excreted. Even in the presence of somewhat impaired renal function, large oral doses have been tolerated. Chronic nephritics have received diuretic doses of 25 gm. of potassium chloride daily[5] and nephrotics, 12 gm. of the citrate and 12 of the bicarbonate daily.[9] Large quantities are routinely used in a variety of other conditions. Although as much as 48 gm. of potassium chloride a day have been given,[14] not more than 10 gm. are well tolerated in a single dose. Larger amounts are followed by elevated serum levels, cardiac effects, paresthesias, and an apparent temporary depression of renal clearances.[12]

Even in the advanced stages of chronic renal disease the renal excretion of potassium is sufficient to prevent the accumulation of a high blood level.[11,18] Toxic effects of potassium have been repeatedly suspected, but in the cases of evident poisoning the symptoms described were almost entirely those from a local irritating effect.[6] Early investigations of the serum potassium in severe nephritis and after experimental nephrectomy have, however, indicated elevated serum levels in a few instances.[10]

Recent studies have thrown new light on the relation of renal failure to potassium intoxication. It has been found that the survival time of anuric rats was decreased by a meat diet, and that the most toxic element in this diet was its potassium content,[1,4] and that a fatal accumulation of potassium occurs in anuric animals even if no food is given.[10]

As would be anticipated from this work, the potassium poisoning in the cases described here was made possible by a nearly complete failure of renal excretion.

Summary. Two cases of fatal potassium poisoning have been described. In one there was a spontaneous accumulation of the serum potassium to 8.85 m.eq./l. and a further elevation to 10.50 after an oral dose of 4.5 gm. of the chloride. The other had been given large therapeutic doses for 5 days. In each there was a failure of renal excretion.

The diagnosis was made by comparison of the findings in these cases with those reported in experimental potassium poisoning, including the serum and urine potassium levels (Case 1), the ECG, and the clinical course. The relationship of paralysis and of renal failure to potassium poisoning was discussed, and the ECG changes leading to arrest of the heart have been shown and described.

The parallel features of these 2 cases illustrating the clinical course of human potassium poisoning were the result of the combined effect of the potassium poisoning and the underlying disease. In each there was: (a) An acute uremia with oliguria; (b) recurrent nausea and retching; (c) episodes of bradycardia unaccompanied by symptoms of

cardiac failure or changes in blood pressure; (d) a sudden ascending flaccid quadriplegia without paralysis of the trunk or disturbance of speech or mental functions; (e) electrocardiographic changes including elevated T waves, absent P waves, intraventricular block, and terminal irregularities of the rhythm; (f) arrest of the heart in diastole prior to the cessation of respiration.

ADDENDUM

Since this report was submitted for publication a third case of fatal potassium intoxication has been encountered. The patient was a housewife of 24 who became anuric as a result of acute nephritis in a single remaining kidney. Flaccid quadriplegia was absent, but death was preceded by the typical sequence of ECG changes and an elevation of the serum potassium level to 10.10 m.eq./l. No potassium salts had been given as such. The case will be reported in detail in a later paper.

REFERENCES

1. ADDIS, T., and LEW, W.: J. Clin. Invest., 18, 773, 1939.
2. ARDEN, F.: Australian J. Exp. Biol. and Med. Sci., 12, 121, 1934.
3. ASTOLFONI, G.: Arch. int. de pharmacodyn. et de ther., 11, 313, 381, 1903.
4. BERGMAN, H. C., and DRURY, D. R.: J. Clin. Invest., 18, 777, 1939.
5. BLUM, L.: Presse méd., Paris, 28, 685, 1920.
6. CASKIE, W. A.: Brit. Med. J., 1, 1052, 1911.
7. DURLACHER, S. H., and WINTERNITZ, M. C.: Yale J. Biol. and Med., 14, 269, 1942.
8. HALD, P. M.: J. Biol. Chem., 103, 471, 1933.
9. HAWES, R. B., and VARDY, E. C.: Quart. J. Med., 4, 1, 1935.
10. HOFF, H. E., SMITH, P. K., and WINKLER, A. W.: J. Clin. Invest., 20, 607, 1941.
11. KEITH, N. M., KING, H. E., and OSTERBERG, A. E.: Fed. Proc., 1, Part II, 180, 1942.
12. KEITH, N. M., OSTERBERG, A. E., and BURCHELL, H. B.: Proc. Staff Meet. Mayo Clin., 17, 49, 1942; also Ann. Int. Med., 16, 879, 1942.
13. MATHISON, G. C.: J. Physiol., 42, 471, 1911.
14. McQUARRIE, I., THOMPSON, W. H., and ANDERSON, J. A.: J. Nutr., 11, 77, 1936.
15. NAHUM, L. H., and HOFF, H. E.: J. Pharm. and Exp. Ther., 65, 322, 1939.
16. NICHOLSON, W. M., and SOFFER, L. T.: Bull. Johns Hopkins Hosp., 56, 236, 1935.
17. PETERS, J. P., and VAN SLYKE, D. D.: Quantitative Clinical Chemistry, Interpretations, Baltimore, Williams & Wilkins Company, 1932.
18. SCHOLTZ, H. G.: Deutsch. Arch. f. klin. Med., 172, 472, 1932.
19. SCUDDER, J.: Shock. Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1942.
20. SMILLIE, W. G.: Arch. Int. Med., 16, 330, 1915.
21. STEWART, H. J., and SMITH, J. J.: AM. J. MED. SCI., 201, 177, 1941.
22. STEWART, H. J., SMITH, J. J., and MILHORAT, A. T.: AM. J. MED. SCI., 199, 789, 1940.
23. STOLL, B., and NISNEWITZ, S.: Arch. Int. Med., 67, 755, 1941.
24. THOMSON, W. A. R.: Lancet, 1, 808, 1939.
25. THOMSON, W. A. R.: Brit. Heart J., 1, 269, 1939.
26. WEBSTER, R. W.: Potassium and the Tartrates: A Review of Their Physiological Effects, Chicago, Commonwealth Press, 1927.
27. WIGGERS, C. J.: Am. Heart J., 5, 346, 1930.
28. WIGGERS, C. J.: Am. J. Physiol., 93, 197, 1930.
29. WILSON, F., and HERMANN, G.: Arch. Int. Med., 31, 923, 1923.
30. WINKLER, A. W., HOFF, H. E., and SMITH, P. K.: J. Clin. Invest., 20, 119, 1941.
31. WINKLER, A. W., HOFF, H. E., and SMITH, P. K.: Am. J. Physiol., 124, 478, 1938.
32. WINKLER, A. W., SMITH, P. K., and HOFF, H. E.: Fed. Proc., 1, Part II, 94, 1942.
33. WOOD, E. H., and MOE, G. K.: Fed. Proc., 1, Part II, 95, 1942.
34. WOOD, J. E., and WHITE, P. D.: AM. J. MED. SCI., 169, 76, 1925.

PROGRESS

OF

MEDICAL SCIENCE

DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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THE TREATMENT OF EARLY AND LATENT SYPHILIS

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The best approach to the modern treatment of early syphilis is a series of short, and to some extent disputable statements indicating landmarks in the progress of the past 35 years. This summary is substituted for the narrative type of historical perspective in this review.

The Mercurial Era. Syphilis therapy up to 1912 left the disease to pursue its physiopathologic course comparatively little influenced at least by the milder and hence most popular forms of medication—the therapy *per os* of the widely copied French school. Even mercury intramuscularly except as the water-soluble salts, and the violently reaction-producing calomel veneered the surface of a syphilitic infection rather than attacked its roots.

The Early Arsphenamine Era. The "therapia sterilisans" period or 1-dose cure era promised by Ehrlich's theorization slowly changed under the impact of criticism from older observers of the course of syphilis under treatment. The belief that something radical, time-saving and treatment-shortening had been accomplished by "606" died hard. One dose was succeeded by successive doses as experience grew. Relatively new conceptions of "cure by stage" came into existence with curious incomprehensible offshoots such as the doctrine of chancre-excision. "Abortive cure," essentially the systematic speculative underestimation of the amount of treatment required by the seronegative primary stage, dates back to this era. From 1916 to 1919 the "course" conceptions of syphilis treatment established themselves, together with a combined theoretical and speculative discussion of the necessity for and the appropriate use of arsphenamine and heavy metal.

The Early Evaluative Period. From 1919 to 1922, an extensive litera-ture, unfortunately not too familiar to some claimants for priorities, con-stituted the initial "shake-down" of an accumulating experiential tradi-

tion. While limited to the serologic effects of treatment and the occurrence of grossly visible forms of relapse as criteria for determining effects, many of the outlines along which the new era has developed were foreshadowed by the reports of Gennerich,[17] the German Dermatological Society (Rost, 1921,[40] Almkvist,[1] Bering,[4] Boas,[7] Hoffmann,[21] Bruck,[9] Jadassohn,[24] Ullmann,[47] Eicke,[15] Hoffmann-Mergelsberg,[22] Müllern-Aspegren,[33] Haxthausen,[20] Rasch,[38] Scholtz[Silberstein[42]], Satke,[41] Mutschler,[34] Zieler,[50] Bruns,[10] Riecke,[39] Bernard,[5] Harrison[19] and others). The stage-of-beginning treatment conception received more or less precise delineation towards the latter part of 1922. A type of foreshortened intensified therapy, that of Scholtz, was reported by Silberstein[42] in 1923, before any American contributions were in the field. When American studies did appear, however, they rapidly established a series of important conceptions, beginning with Moore and Kemp's[31] demonstration based on Keidel's[30] foresighted Johns Hopkins system, of the importance of continuity in treatment, and S. W. Becker's[2] demonstration at the Mayo Clinic of the value of massing or intensification of arsenical therapy at the moment treatment is begun. Familiar to Americans during this period are the Pollitzer-Ormsby[35,37] variation on the Scholtz technic and other types of intermittent systems which lost ground after the League of Nations confirmation[28,46] of the substantial superiority of continuous treatment.

The League of Nations Syphilis Commission Evaluations.* Begun on a massive scale in 1928 with conclusions and recommendations stated in 1935, this world-wide survey of technical methods in the treatment of early syphilis provides the basis for what may now be spoken of as the conservative or prolonged method for the treatment of early and latent syphilis. Under the terms of the coöperative agreement among the nations participating, each was individually encouraged to make the most of his own material in addition to contributing to the general pool. This rapidly brought American material into the foreground, and the contributions of the Cooperative Clinical Group[13] working under the ægis and with the statistical coöperation of the United States Public Health Service, express today what might be called the basic formula of American practice. From the League of Nations evaluation for which Martenstein supervised the interpretations,[28] two general systems of treating early syphilis emerged —the British-Scandinavian intermittent and the American continuous systems. A certain amount of argument has inevitably arisen over the suitability of the material for deciding the question of intermittence *versus* continuity, but on the whole the Commission's findings seemed to justify the belief that the intermittence of the recommended intermittent system is more formal than actual and that its intensity especially in simultaneous arsenical and heavy metal administration, causes its effects to be substantially those of a somewhat less intensive but continuous technic. Enthusiasm for the newer foreshortened procedures (see below) should not be allowed to dim the significance of this great evaluative accomplishment, and the syphilologist of today may without hesitation subscribe to either of the announced conservative systems as the equal in curative

* Under the direction of the League of Nations Health Organization, the following countries participated: Denmark, France, Germany, Great Britain, United States of America. The membership in 1928 included Jadassohn (Breslau), Chairman, Madsen (Copenhagen), Colonel Harrison (London), Queyrat (Paris), Stokes (Philadelphia), Rasch (Copenhagen); Gougerot replaced Queyrat, Lomholt replaced Rasch in 1935. Statistical consultant, Westergaard (Copenhagen). Evaluation and report by Martenstein (Dresden).

effect of the more recent "hurry-up" systems of procedure with a substantially greater margin of safety.

Since the League of Nations evaluation has established such substantial landmarks, it may well be used as a milestone at which to summarize the high points of the progress of syphilotherapy since the close of the mercurial age. The following fundamental principles have emerged from a quarter century of revolutionary progress:

1. *Early and not late syphilis is the domain of systems.* Bad effects follow haphazardness, short courses, low dosage and lapse from treatment in early syphilis.

2. The *"stage at which treatment is begun" principle* is established with trustworthy evidence that seronegative primary syphilis is the most easily cured of all stages of the disease, seropositive primary syphilis the most uncertain or resistant and secondary syphilis midway between the two.

3. *Relapse follows short treatment,* especially arsenical, producing delayed secondaries, neurorecurrence, infectious mucosal lesions, serologic relapse and fastness.

4. *Single drug treatment is inferior to combined treatment* and a heavy metal improves arsenical results and compensates shortcomings.

5. *Prolongation*—more injections, longer courses—gives superior results in systems dominated by the calendar interval of 1 week. Prolongation and increased mass through individual and total dosage were, of course, attempts to meet the resistance of the 30% relapsing group among early syphilitics at large.

6. *Dosage theory* was spotted with empiricism. The concept of lower drug tolerance of the female as compared with the male; the large *versus* small dose school; the crowding or time-dose problems represented by the so-called intensive method; the toxicity fears (simultaneous *versus* alternate administration of arsenical and heavy metal); the idiosyncrasy and technical error factors in reaction interpretation which held down dosage, while reports of relapse and resistance raised it.

7. *Calendar servitude* or the domination of the 7-day interval on a purely empirical unevaluated basis was general. Few ventured to think in terms of shorter intervals or would admit their practicality or desirability.

8. *Rising appreciation of scheduling.* It became clear that schedules or systems critically examined by large syphilologic centers and expert experience were the sound basis for treatment methods rather than the results of blood serologic tests, thus slowly displacing the serologism of the 1920's.

9. *The vital comprehension of toxicity and therapeutic efficiency relations* was dominated by the laboratory and rested on the insecure foundation of trypanosomiasis in mice rather than syphilis in man or animals. This group of conceptions, though expressed by impressive numerical indices was essentially vague and inadequate. A true experimental basis for syphilotherapeusis did not yet exist.

10. *Despite these strictures on the knowledge of the day,* the work of individual investigators plus the League of Nations evaluations established the following facts:

(a) *An arsphenamine alone can "cure" early syphilis* in a large percentage of cases."

(b) *Heavy metal is a potent augmenting force,* particularly true of bismuth; a fact recently "re-discovered" by recent workers with intensive methods.

(c) *Arsenical therapy can be "crowded"* or "foreshortened" without fatal effect and with good results (Scholtz-Silberstein massive divided dose system).

(*d*) *Continuity and calendar regularity* are vitally important to the conservative or prolonged systems evaluated by the League of Nations. "A little treatment continuously given is twice as effective as the same amount of treatment intermittently given."

(*e*) *Prolongation of treatment* (in the weekly calendar or conservative systems) irons out most complications, relapse and resistance.[3]

(*f*) *Some important League of Nations and Cooperative Clinical Group principles:*

(1) The curative outlook is one-third better when treatment is begun in the seronegative primary stage than in other stages of early and and latent syphilis.

(2) The good results obtained by prolonging continuous treatment longer than 1 year more than double those obtained by the same kind of treatment carried through less than a year.

(3) Intermittent and irregular treatment are the principal sources of delayed reversal of the blood serologic reaction.

(4) Prolongation and intensification of treatment, using much arsphenamine and heavy metal, but especially much arsphenamine in the first 3 months promotes good results.

(5) Satisfactory results may occur with little treatment, but much treatment and over prolonged periods is twice as effective as little treatment if continuously applied, and 5 times as effective as treatment intermittently applied.

(6) Arsphenamine is the chief factor in relapse prevention, and this applies specifically to the incidence of neurosyphilis (note importance of this principle in foreshortened intensive methods).

(7) Serologic irreversibility becomes the more marked the later in early syphilis treatment is begun, and the more frequently lapse from continuity occurs whether in the form of rest intervals or otherwise.

(8) A weak positive serologic reaction interrupting a series of negatives in early syphilis is a distinct warning of the possibility of relapse.

Much of the effectiveness of the foreshortened intensive treatment methods was predicted by Martenstein's conclusions from the general League of Nations material that the employment of a comparatively heavy individual dosage of the arsenical and of bismuth or mercury with administration in rapid succession at the outset of treatment, leads to superior results. Furthermore, approximately the same amount of treatment should be administered to primary as to secondary cases.

(*g*) *Large dosage is preferable to small;* should follow a weight standard, and be without sex differentiation.

(*h*) *Many of the most serious complications of treatment* are due to background causes (idiosyncratic-allergic, intercurrent infections, and technical factors rather than the drugs as such alone). In particular, the combination of arsenic and bismuth is as safe as arsenic alone.

(*i*) *To date, no claims for the use of a heavy metal alone* in the treatment of early syphilis have withstood critical evaluation. An arsenical is essential as a controller of infectiousness. The effect is augmented by bismuth, and also though probably less so, by mercury. Twenty full doses each of arsenical and heavy metal approximate a minimal amount of treatment for infection control (so-called 20–20 standard).

(*j*) *The controversies over the individual merits of arsenicals* (606, 914 and so forth) have been largely submerged by the overwhelming popularity of

mapharsen in American practice, due largely to its low toxicity, combined with high spirillicidal value. This has been overwhelmingly demonstrated in the 5-day massive dose arsenotherapy (5-day drip) and its therapeutic efficacy when intensively employed has also been demonstrated by the Eagle-Hogan animal experiments.

Additional Basic Principles for Present and Future Emphasis. 1. The Boeck[11] material underlies the principle that *syphilis "cures" itself* in 40% of cases.

2. A little treatment in early syphilis[36] raises the percentage of cure another 20% to 30%.

3. *Intensification and prolongation* (or repetition in the case of intensive foreshortened methods) directed at the resistant 30% bags another 15% to 25%, depending on stage-of-beginning-treatment, for cure.

4. *The remaining 5% to 15%* represents the irreducible residue of resistance (deficient defense, special strains and so forth) that nothing save time, therapeutic repetition and variation, and fever, if anything, will cure.

5. *Non-specific agents* (fever) have important re-enforcing and curative effects in early as well as late syphilis—chiefly by enhancing the effectiveness of arsenicals faster than it increases their toxicity.[6]

6. *The spinal fluid examination* is an indispensable evaluative and curative check procedure more important ultimately than blood serology.

7. *As to observation and discharge as cured*, all patients who have had an entirely non-relapsing course while receiving ideal treatment should be informed that a cardiovascular reëxamination in the 5- to 10-year period is necessary.

8. *The syphilitic pregnant woman* or the woman who has had syphilis and is believed to be cured should have her status reviewed with every pregnancy and safety-first requires her treatment for protection of the child during each pregnancy whether seronegative or seropositive.

9. *Unsatisfactory results* (non-cure) are usually reviewed by the 5th year of observation and Padget found no less satisfactory results in any case after 10 or more years of observation.

Principles Established by the Clinical and Experimental Study of Foreshortened Intensive Methods. The past decade of work with intensive treatment methods has contributed a number of additional important principles to our understanding of syphilotherapy.

1. Hyman and his co-workers[16] have demonstrated that an approximation to the *total curative dose of an arsenical can be administered to a human being* by an intravenous infusion method (drip) without necessarily disastrous effects with a controllable though increased toxicity and with satisfactory results.

2. *A toxicity-therapeutic efficacy relationship* has been worked out by Eagle and Hogan[14,16] on the basis of animal, and more recently human clinical results. Syphilis can be cured in 80% to 100% of cases (stage-of-beginning-treatment factor) by a total dose of 20 to 30 mg. per kilo body weight of an arsenoxide (mapharsen) alone.

3. *The toxicity of such a dose* is inversely proportional to the time in which this dose is given.

4. *Any combination of toxicity and time relationship* (that is, any margin of safety) that practical considerations may dictate is theoretically possible, the mortality rising with the shortening of the time in which the total dose is delivered.

5. *The addition of bismuth* ("re-discovery") *greatly enhances the effect of*

all foreshortened intensive arsenotherapy (informally estimated by Eagle as 8 times better effect with bismuth than without).

6. *Serologic signs and symptoms* under foreshortened procedure disappear gradually on a now well-recognized gradient to which a quantitative serologic procedure is essential in interpretation.

7. *A wide variety of time and technical variations* (5-day intravenous drip *versus* 10-day multiple injection, *versus* 10 to 12 weeks of 2 to 3 injections weekly, *versus* 26-week schedules) with graded morbidity and mortality but substantially identical therapeutic outcome can be employed as forms of "foreshortened intensive" systems in the name of various types of exigency or expediency.

8. *The mortality of the 5-day drip* is currently estimated at 1:200 to 1:300. Any schedule completed in 20 days or less will have a mortality greater than 1:1000 (Eagle-Hogan); 10- to 12-week systems have a mortality of approximately 1:1500. The mortality of 20- and 26-week systems is not yet definitely known. That of reasonably good performance of the standard conservative prolonged systems is estimated by Hahn[18] (Johns Hopkins Hospital) at 1:1950; with optimum experience at 1:2800. It must be recalled that the mortality of conservative treatment is computed from arsphenamine and not mapharsen-treated cases. The toxicity of mapharsen is so low (1 death in 3938 patients[16]), that a material drop in mortality should follow its use in the conservative systems. Levine and Keddie estimate the mapharsen death rate to be $\frac{1}{2}$ that from neoarsphenamine.

9. *The foreshortened intensive procedures* (up to 12 weeks) greatly reduce the incidence of neurosyphilis.

10. *The justification of the foreshortened procedures* except for their apparent efficacy in the prevention of neurosyphilis (spinal fluid abnormality) is in the main still one of emergency and expediency. The ultimate results are obtainable by the older slower methods with less risk of life. What effect this will have on their post-war use remains to be seen.

In a discussion of the basic principles of system evaluation applicable to foreshortened intensive methods, Stokes[43c] wrote as follows:

"Any new systems proposed should be judged basically by their ability (*a*) to equal or surpass the 'curative' expectancy of the old ones; (*b*) to lead to less infectious relapse; (*c*) to reduce the incidence of cardiovascular and neurosyphilis, and (*d*) by their relative risks to the patient.

"For the evaluation of a system, time and observation are necessary to establish reduction of, or absence of relapse and progression. For the former, 2 to 4 years; for the latter, up to 10 years is a reasonable observational requirement. For decision on relapse the patient must be repeatedly and frequently observed, for it is a *come and go affair*. For the evaluation of 'cure,' from a decade to a lifetime, the longer the better, is required.

"A system which under such scrutiny has shown itself at least equal to its predecessors may then proceed to claim additional advantage and support for a variety of reasons, including cheapness, rapidity, controllability of the lapse factor because the whole job is finished in a short time, aid in the widening of availability of treatment by making possible the treatment of more persons per unit of time, personnel and equipment. Such considerations are in the main secondary to those of control of infectiousness and real curative power.

"If the new system equals the old or surpasses it in all these particulars it has but one more hurdle to make before achieving priority. While

primum non nocere is losing some of its meaning in a war-torn world, there are still arch conservatives who are inclined to examine critically the bad effects, the complications of a system. Of real importance to the victim are the risks involved, the chances of damage or of death from treatment in the case of a disease which with none or very little treatment gives the victim at the outset a 40 to 70% chance of escape from serious consequences. If an equal chance of escape with an older method offering less risk exists, only the most cogent reasons and a free choice by the patient of the more dangerous method justify its election."

The Conservative or Prolonged Standards of Treatment for Early, Early Latent and Late Latent Syphilis. It is now in order to summarize what may be called the "official" or most widely authenticated and accepted systems for use in that phase of the disease which permits of systematization in procedure. While it is impossible, with the rapid changes taking place in syphilotherapy, to predict how long such systems will have a following, it should be clearly understood that they are effective, and will do all that the foreshortened systems will, with a very much greater margin of safety. To the British-Scandinavian intermittent system[8] (which must be exactly followed, diagram in hand) and a slight but now, for American practice, "official" modification of the American continuous (League of Nations) system, the "30-60-03,"[43] is added the as yet unproved and unevaluated but rational "Army Plan" recommended to the Surgeons General by the National Research Council and publicized in Circular Letter No. 74. The conservative systems are still, we believe, the backbone of modern practice, the basis of much of our present knowledge of mechanism and effects, and likely to be displaced completely only by certain radical changes in the whole chemotherapeutic attack on the disease such as are affecting the pyogenic infections, gonorrhea, etc. (the sulfonamides, penicillin).

The British-Scandinavian (League of Nations) System: Plan of Courses of Injection.

A course consists of 8 weekly injections of neoarsphenamine (0.6 to 0.75 gm. each) or arsphenamine (0.4 to 0.5 gm. each) given simultaneously with 8 weekly injections of an insoluble bismuth compound (0.2 to 0.24 gm. bismuth metal each) and followed by 2 more weekly injections of bismuth compound. An equivalent amount of a mercury preparation may be substituted for the bismuth (inunctions for 40 days at 3 gm. of unguentum hydrargyri or injections of 70 mg. of mild mercurous chloride or 120 mg. of mercuric salicylate, etc., suspended in a suitable base). It is recommended that:

(*a*) In cases which remain or become serologically negative during or by the end of the first course, 4 such courses be administered, with intervals of 3 to 5 weeks between any 2 courses.

(*b*) In cases which have not become seronegative by the end of the first course, in addition to the amount of treatment shown in (*a*), further courses should be administered until the patient has received as a minimum 3 beyond that which has ended with negative serum reactions. At the option of the individual clinician, this treatment may be prolonged as may be considered necessary.

(*c*) Cases presenting signs of clinical relapse of an early type should be dealt with on principles similar to those enunciated in (*b*).

For non-pregnant females, treatment should be administered on the plan outlined for men, with the exception that the single dose of neoarsphenamine should be reduced by 0.15 gm. and that of arsphenamine by 0.1 gm.

In the event of any reduction in the amount of treatment being indicated, it is recommended that this be effected by reducing the number of arsenical injections rather than by reducing the individual dose or increasing the intervals.

The American Continuous System: The "30–60–03" "Official" Modification, Circular Letter No. 18 of the Surgeon General's Office, U. S. Army. The published work of the United States Public Health Service and the Cooperative Clinical Group in the United States has indicated that continuous treatment with an effective arsenical alternating with bismuth on a definitely defined schedule with calendar regularity and without rest periods during the arsenical phase is the optimum conservative technic for the treatment of seronegative and seropositive primary syphilis, secondary syphilis, and early latency (within the first 4 years of the infection when the duration is known). An essentially similar standard of treatment employing 606, parallel with an acceptable intermittent (British-Scandinavian) system of treatment employing neoarsphenamine, has been recommended by the Commission on Syphilis and Cognate Subjects of the League of Nations as a result of an extended study of an international statistical material. It may therefore, it is believed, be accepted as having the support of authority.

For mnemonic convenience, the designation, "30–60–03" is suggested, for the standard system for early and early latent syphilis;[43] the "30" representing the number of arsenical injections; the "60" representing the number of weeks of bismuth therapy, equivalent to 60 injections of bismuth subsalicylate, and the "0" and "3" representing respectively, no rest periods, and 3 years of combined treatment observation. By "treatment observation" is meant the total elapsed time from the institution of treatment in accordance with this schedule until the patient is discharged from observation as presumptively cured.

Since the sequence of various types of treatment in this system, the prevention of relapse by overlapping of heavy metal and arsenical therapy, the serologic controls, the spinal fluid examination, all are integral parts of the treatment system, the following diagram is offered as presenting these various relationships.

The "30–60–03" for Early Syphilis.
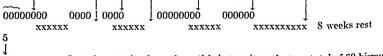
30 neoarsphenamine or mapharsen injections, 60 weeks of bismuth injections.
NO rest intervals in the arsenical phase, 3 years of treatment observation.
0 = neoarsphenamine or mapharsen; x = bismuth subsalicylate; weekly intervals.

```
     A    1           B    2      C        3           4             D
       ↓              ↓   ↓      ↓        ↓                          ↓
   00000000      0000 ↓ 0000    ↓ 00000000       000000             ↓
       xxxxxx             xxxxxx            xxxxxx        xxxxxxxxxx   8 weeks rest
   5
   ↓
   xxxxxxxxxx   8 weeks rest (and continue this intermittently to a total of 60 bismuth
       injections).
```

A = first 3 injections compressible into 10 to 14 days. Some risk of increased reactivity.
B = average case seronegative, 16th week.
C = Examine spinal fluid if blood is still positive, 24th week.
D = Always insist on spinal fluid examination before rest period.
1 = if blood test has become negative, suspect low resistance.
2, 3, 4, 5 = if weak positives appear among negatives, suspect relapse, neurosyphilis.

The "30–60–03" schedule as thus presented can be drawn up in "vertical" as distinguished from the above "horizontal" arrangement, week by week, for printing directly on record forms.

The published observation of the USPHS–CCG group on the treatment of early syphilis indicated that the "30–60–03" schedule could be most effectively applied to seronegative primary syphilis and fully developed secondary syphilis. In the case of seropositive primary syphilis, whose status should be confirmed in the seronegative cases by a repetition of the blood test on the day following the first

arsenical injection, there were definite indications that the seropositive primary phase of the disease, lacking the development of a full-fledged immunity reaction on the part of the body was the most resistant to cure, and the most prone to relapse of the 3 groups of cases included under the designation, "early syphilis." It has accordingly been proposed that in seropositive primary syphilis and initially negative primary syphilis which becomes seropositive on the blood immediately following the institution of treatment, a "40–80–04" system be employed, meaning thereby an additional 10 arsenical injections and 20 bismuth injections and another year of observation over and above the standards proposed as generally applicable to early and early latent syphilis. This extension of the arsenical phase of treatment can take the form of 5 courses of the arsenical of 8 injections each, in place of the 3 courses of 8 and 1 course of 6 injections in the "30–60–03" system. The bismuth therapy may follow the usual 2-injection overlap, plus 4 additional injections in the arsenical intermission that is employed in the "30–60–03"; the remaining bismuth injections to complete the 80-week standard, being continued in 10-injection intermittent courses after the completion of the arsenical phase of treatment.

The 26-Week Army System. The diagram is adapted from Circular Letter No. 74, Surgeon General's Office, U. S. Army.

Week	Arsenoxide	Week	Bismuth
2		1	
2		2	Bismuth subsalicylate
3		3	intramuscularly once
4	Arsenoxide intravenously	4	a week, 5 injections
5	twice a week; total 20	5	
6	injections	6	Omit bismuth subsalicyl-
7		7	ate 5 weeks
8		8	
9		9	
10		10	
11		11	
12		12	
13	Omit arsenoxide 6 weeks	13	Bismuth subsalicylate
14		14	once a week, 6 injec-
15		15	tions
16		16	
17		17	
18		18	Omit bismuth subsalicyl-
19		19	ate 5 weeks
20	Arsenoxide as in first	20	
21	course twice a week;	21	
22	total, 20 injections	22	
23		23	Bismuth subsalicylate
24		24	once a week, 5 injec-
25		25	tions
26		26	

Dosage. Arsenoxide, 0.05 to 0.07 gm., based on patient's weight. Bismuth subsalicylate, 0.2 gm. (Forty injections arsenoxide—16 bismuth subsalicylate.)

Serologic Control of Treatment. In patients with early syphilis treated with the Army system, a serologic test will be done at the beginning and end of the schedule of treatment outlined but treatment may be stopped whether the serologic reaction for syphilis is positive or negative. After the completion of treatment the serologic tests should be repeated 3 and 6 months later. If the reaction is negative after 6 months, the case may be classified as "result satisfactory" and the *Syphilis Register* may be closed. If the test is positive after 6 months, the patient should be referred to a station or general hospital.

In patients with latent syphilis the serologic tests should be repeated at the completion of the treatment outlined, but the *Syphilis Register* may be closed when this treatment is completed, regardless of the result of the serologic test.

Spinal fluid examination should be performed in a hospital in patients with early syphilis at the end of the course of treatment outlined, or as soon as possible there-

after, but in any event before the *Syphilis Register* is closed. In apparent latent syphilis, spinal fluid examination should be performed in a hospital before treatment or as soon as possible thereafter, but in any event before the *Syphilis Register* is closed.

A System of Treatment for Latency—"24–60–100 plus." Before defining a system by which adequate treatment of latency may be judged, it must be reëmphasized here that the latency implied is "monosymptomatic seropositive latency" in which absolutely no clinical evidence of syphilis can be identified on complete physical examination except the positive and confirmed—and confirmable—blood-serologic reaction for the disease. An adequate examination of the spinal fluid is necessary to establish the fact that a seeming latency is not complicated by asymptomatic neurosyphilis. A patient who has been adequately treated for an early syphilitic infection but who still remains seropositive on the blood in order to be considered as in monosymptomatic seropositive latency (serologically fast) should have had a negative spinal fluid 1 year after the close of his treatment for early syphilis, and if more than a year has elapsed since the cessation of such treatment, a repetition of the spinal fluid examination is desirable. A long series of negative spinal fluids is not necessary to the establishment of the status of monosymptomatic seropositive latency, for according to USPHS–CCG observation, more than 1 or 2 repetitions of a negative fluid in the absence of any developing clinical signs is unnecessary.

The latency of a syphilitic infection is divided arbitrarily into an early and a late period, partly because of the greater risk of infectious relapse and other types of recurrence in early latency, and partly because of the presumed better outlook for complete arrest if not cure in the earlier years of the latent period. The dividing line between early and late latency has tended in American practice to be the fourth year of the disease. This is an arbitrary setting which may in the judgment of an expert, be varied one way or the other. A young and robust person whose infection is of 5 or even 6 years presumed duration may be advised to accept the standard for an early infection in his treatment. On the other hand most genuine latency, after the 4th year, shows relatively little tendency to progression, and may be treated by a standard substantially lower than that proposed for the radical cure of early infection.

The treatment of early latency (first 4 years of the disease) is that of early syphilis—the "30–60–03" system.

The Cooperative Clinical Group's[13] experience has indicated that for the treatment of late latency (after the 4th year) 3 courses of 8 injections each of an effective arsenical given in continuity and alternation with 10 injections of bismuth subsalicylate, without overlap and with continuity extending only through the arsenical phase, constitute an adequate beginning. The continuous treatment with arsenical and heavy metal is then followed by an intermittent and prolonged treatment with bismuth alone which should total, including the three 10-injection bismuth courses given with the arsenical phase, not less than 60 weeks of bismuth therapy. Further treatment with bismuth to the extent of 80 weeks, or even 100 weeks, or on the basis of 80 weeks, plus "a course a year" for several years, was found to increase appreciably the good results by the criteria employed. It is not necessary, however, in judging candidates for admission to the services, to insist on prolongation of the heavy metal phase beyond the 60th week. Approximately 70% of monosymptomatic seropositive latency may be expected to reverse to negative on the blood for an indefi-

nite period following a 24–60 course, and the failure of the remaining 30% to reverse may be regarded as no bar to eligibility.

As a general principle, late latent cases remaining seropositive after a 24–60 course should be observed at intervals of a year or two with physical examination and appropriate tests for evidence of cardiovascular progression and ultimate neurosyphilitic involvement.

It should be emphasized that late latency is usually much overtreated on the basis of fluctuating positive blood serologic reactions alone, or because of conflicts between the results of various laboratories ("serologic discord").

Massive Dose, Foreshortened Chemotherapy of Eealy Syphilis, Description of Procedure, Indications and Contraindications. All methods of intensive therapy are intended for patients with early syphilis (primary, secondary, relapsing secondary, and early latency) who have received little or no previous therapy, who are robust young people, especially men, reasonably free from serious visceral disease, particularly hepatitis, myocarditis, severe hypertension, nephritis, excessive alcoholism, blood dyscrasias, active pulmonary tuberculosis, and history of previous serious arsenical reaction. Although it is safe to administer sulfonamides simultaneously with conservative prolonged therapy and even with the 12-week system, it is unsafe to give sulfonamide therapy for gonorrhea or other conditions to patients receiving 5- to 10-day intensive therapy.

Pre-treatment Routine (All Methods of Intensive Chemotherapy) (after Leifer, 1940[16]). The routine examination consists of the following: 1. Daily urinalysis, including determination of urobilin.

2. Determination of the urea nitrogen content of the blood and the icterus index.

3. Complete blood count, including that of the platelets.

4. Complete physical examination on admission.

5. Serologic examinations made in 3 different laboratories (these include the Kolmer, Kline diagnostic, Kline exclusion, Kahn standard and titered Wassermann tests).

6. Dark-field examination of material from all open sores.

7. Estimation of renal function by determination of the specific gravity of the urine.

8. Special tests of hepatic function by the bilirubin method.

9. Studies of the excretion of arsenic in the urine and in the stool and its concentration in the blood (optional; for study purposes).

Technic of 5-Day Intravenous Drip (Chargin, Hyman, Leifer[16]) (after Committee on Massive Drip Intravenous Therapy, 1940). *Materials·* 1. Needle—deep injection type, No. 20, 1½ inch length.

2. Diluent—5% dextrose solution.

3. Drug—mapharsen (arsenoxide), ampoules 0.04, 0.06, and 0.06 gm.

4. Glass gravity cylinder, 300 cc. capacity with attached rubber tubing, glass drip chamber, adapter for needle. Vacoliter or similar container may be used instead of apparatus described (L. W. Shaffer).

5. Adhesive or Scotch tape (½ inch width).

Dosage of Mapharsen: 1. Total dosage for the 5-day treatment period is determined by the stripped weight of the patient. In patients weighing less than 70 kg. (155 pounds) the total dose is 1000 mg. (1 gm.); in those weighing 70 kg. or more, the total dose of mapharsen is 1200 mg. (1.2 gm.).

2. The daily dose is 200 mg. (0.2 gm.) for patients receiving a total of 1000 mg. (1 gm.).

3. The daily dose is 240 mg. (0.24 gm.) for patients receiving a total of 1200 mg. (1.2 gm.).

4. If a patient receives less than the intended daily dose (this will most often occur on the first day of therapy), the deficiency in dosage may then be spread over the remaining days of treatment. Thus, if the patient receives 120 mg. (0.12 gm.)

the first day instead of the intended total daily dosage of 240 mg. (0.24 gm.) he may be given 30 mg. (0.03 gm.) additional on each of the succeeding 4 days of treatment.

Procedure: Site of Election for Insertion of Needle. After cleansing of forearm and application of a tourniquet above the elbow to distend the veins, the needle is attached to a 2 cc. Luer type syringe and inserted in a vein on the forearm, usually anterior or outer aspect, between elbow and wrist, to allow movement at these articulations. Needle should be inserted into vein up to the hub, a gauze sponge placed beneath the needle hub, and the needle fixed in place with adhesive (or Scotch) tape. Alternate arms on succeeding days.

The adapter of the intravenous set is attached to the needle (after the adapter has been freed of air bubbles) after the removal of the tourniquet, and the solution is allowed to flow rapidly until 10 to 15 cc. have entered. Should any swelling or infiltration be noted about the needle point, the flow should be stopped; the needle removed, and reintroduced into a different vein in the same or opposite forearm. The rate of flow is regulated by the fine adjustment clamp so that solution enters at a speed of about 50 to 60 drops per minute; thus, the entire quantity of 2000 cc. will require 8 to 12 hours for introduction.

Addition of Bismuth to Massive Dose Technic. Since July, 1941, L. W. Shaffer has been using bismuth concurrently with the arsenical. It may be used as follows:

Dosage of Bismuth With Intravenous Drip Method: 1. Suspension of bismuth subsalicylate in oil is employed.

2. The patient should receive 0.2 gm. bismuth subsalicylate (0.13 gm. bismuth metal) intramuscularly as soon as the diagnosis of early syphilis has been confirmed.

3. The second dose of 0.2 gm. should be given on the 3d day of treatment, the third dose of 0.2 gm. on the 6th day and a fourth dose of 0.2 gm. on the 9th day, before discharge.

Method of Preparing Arsenoxide Solutions. Mapharsen (arsenoxide), 0.01 gm., is dissolved in 100 cc. of 5% dextrose solution. Usual procedure is to prepare 500 cc. of such solution, containing 0.06 gm. mapharsen—this is enough for 3 hours of treatment.

When the Vacoliter containing 2000 cc. of 5% dextrose is used, the total daily dose of 0.24 gm. mapharsen (arsenoxide) is prepared the first thing in the morning and the solution allowed to run in, in the 10 to 12 hour treatment period.

This has been the practice in one institution. The preparation of the drug for the 10 to 12 hour period all at once has simplified the technic to a great extent.

Variants in Usual Procedure: 1. Primary fever on the 1st day (Herxheimer)—therapy is stopped if temperature reaches 101.4° F. or more. This usually happens between the 6th and 8th hour; by the time patient may only have received from 0.12 to 0.16 gm. mapharsen. The practice has been to compensate for this insufficient dose in the following manner: 1st day—0.12 gm. mapharsen (arsenoxide); 2d day—0.28 gm. mapharsen (arsenoxide); 3d day—0.28 gm. mapharsen (arsenoxide); 4th day—0.28 gm. mapharsen (arsenoxide); 5th day—0.24 gm. mapharsen (arsenoxide).

2. Clinical jaundice—when this appears in the course of treatment, the procedure should be interrupted. It has only been seen once in all cases studied (Committee report).

General Medical Care During 5-Day Intravenous Drip. Routine soapsuds enema should be given the night before treatment is begun, to obviate the need for bedpan, and whenever thereafter indicated. According to Leifer's (1940) description: "The nursing problem during the period of treatment consists of the preparation of fresh solution for each patient at the end of 2 or 3 hours and the refilling of the gravity flask. Meals are served on the ordinary bed tray. Patients can feed themselves. They are also capable of handling the urinal but, naturally, must be assisted somewhat in the use of the bedpan. The latter disturbance may be prevented by having the patient evacuate or have an enema during the evening, when treatment has been discontinued.

"The patients are given a high calory diet, rich in starches and carbohydrates. The majority of the patients read, listen to the radio, or play cards during the day. In the evening, after discontinuance of therapy, they may get out of bed. They

suffer little or no discomfort. Many of them register a gain in weight of as much as 10 pounds (4.5 kg.). This gain in weight is not due to any appreciable edema but may be explained by the fact that most of these patients otherwise under-nourished, are so well treated with regard to food and nursing care."

Technic of 10-Day Multiple Injection Intensive Therapy for Syphilis.[16] With this treatment system patients need not be confined to bed, but they should be treated in the hospital and observed for at least 2 days after the last injection of mapharsen (arsenoxide). Routine ward diet may be employed.

Two injections of mapharsen (arsenoxide) are given daily for a 10-day period. The injections are given in the morning and evening of each day, 10, or preferably, 12, hours apart. Schoch, however, has given single injections of 100 to 120 mg. daily as an ambulatory procedure. Dosage is governed roughly by weight. Patients weighing 50-70 kg. (110 to 154 pounds) should receive 0.05 gm. of maphar-sen twice daily for 10 days. Patients weighing between 70 and 90 kg. (155 to 200 pounds) should receive 0.06 gm. of mapharsen twice daily for 10 days. The dosage may be increased to 0.070 gm. in each injection for patients weighing over 90 kg. (200 pounds). Each dose of mapharsen (arsenoxide) should be dissolved in from 8 to 10 cc. of distilled water. The *solution should be aerated* and *rapidly injected*, intravenously, promptly after preparation. In cases where solutions are made in bulk, individual doses should be given within at least a 2-hour period after preparation.

On the 1st, 4th, 8th and 12th days, 0.2 gm. of bismuth subsalicylate in oil should be injected deeply into alternate gluteal muscles.

Thomas and his associates of Bellevue Hospital combine fever therapy with the intensive multiple syringe technic (1941, 1943). The risk of serious cerebral accidents with this method increases with the amount of arsenoxide (mapharsen) given. The addition of fever does not prevent cerebral reactions but lessens their frequency by necessitating a lower dosage of arsenical.

Reactions from 5- to 10-Day Intensive Therapy and Their Management. Minor Reactions: 1. *Pain in the arm:* cold wet dressings, ice-bag, aspirin, codeine only if pain is severe.

2. *Mild headache:* aspirin or codeine usually gives prompt relief. If headache is severe, increasing and persistent, consider this as possible prodrome of toxic encephalopathy.

3. *Nausea and vomiting:* give only fluids by mouth, and sedation if necessary. If persistent, discontinue treatment temporarily. May give 5% or 10% dextrose solution alone intravenously.

4. *Primary fever:* sharp rise in temperature occurs on the 1st day of treatment especially with intravenous drip. It is usually almost normal by evening, and normal by the next day. If the temperature goes above 101.4° F. discontinue drip for the day. Next day, drip may be rein-stituted, practically always without recurrence of fever; this early fever need not cause omission of the second dose when multiple syringe method is used. Primary fever is usually accompanied by a flare-up of the syph-ilitic lesions (Herxheimer reaction, therapeutic shock). Symptomatic treatment may be used if necessary.

5. *Secondary fever:* secondary rises of temperature in excess of 101° F. at any time after the first day of treatment are an indication for interrupt-ing therapy because secondary fever is sometimes associated with a mild toxicoderma. Most often in the 5-day treatment the fever occurs on the last evening of therapy. Mapharsen should not be given again until the temperature is normal. If fever recurs when treatment is reinstituted, efforts at intensive therapy should be abandoned entirely.

If the patient has received at least a total of 800 mg. (0.8 gm.) of maphar-sen (arsenoxide) before the appearance of fever, intensive arsenotherapy by any system should not be reinstituted. In this case all further arsenical

therapy may be omitted, but the patient should receive a total of at least 12 weekly intramuscular injections of bismuth subsalicylate before all treatment is stopped.

Symptomatic treatment for this reaction may be used, if necessary.

6. *Toxicoderma:* usually appears in the post-treatment period on the 7th day, and is often preceded by and accompanied with fever. The type is most commonly morbilliform, scarlatiniform, or urticarial, and there is no exfoliation. This is not arsenical exfoliative dermatitis, and is not a serious sensitizing reaction. The rash usually fades in $1\frac{1}{2}$ to 4 days without therapy. Symptomatic treatment may be used, when indicated.

Since this reaction does not usually occur with the intravenous drip method until all treatment has been completed, it has no bearing on interruption of such treatment. When the 10-day multiple injection system is used, the occurrence of this "9th-day erythema" is an indication for interrupting treatment. This reaction may be associated (rarely) with toxic encephalopathy, and continued treatment may increase the risk.

7. *Renal damage:* usually insignificant, consisting of minor traces of albumin, occasional red and white blood cells. No treatment is needed.

Marked albuminuria or hematuria is a signal for discontinuing treatment.

8. *Peripheral neuritis:* rarely encountered, and only in the post-treatment period. Usually manifested only by subjective symptoms, most often paresthesias. Objective changes are rarely encountered, and only sensory in type, never motor. The process disappears spontaneously. This reaction was common in the cases treated early by the 5-day method, probably because of immobility of the arm and the use of a drug too toxic (neoarsphenamine) for such a method.

9. *Nitritoid reaction:* rarely observed with multiple injections or with the intravenous drip procedure, unless the rate of flow of the latter is inordinately fast (mapharsen [arsenoxide] is well known to produce this reaction only rarely).

10. *Precordial oppression* (Falk and Rattner, 1942; Prats, Veras and Haraszti, 1942): this occurs occasionally with 5-day treatment. Disconcerting but not frequent or serious.

Major Reactions: 1. *Severe headache:* especially towards the 4th or 5th day of treatment, the occurrence of severe, persistent and increasing headache not readily relieved by aspirin or codeine should be viewed as of possible serious import (prodrome of toxic encephalopathy). It is best to discontinue intensive therapy and after a rest interval from all arsenical therapy of at least 4 weeks (this rest period to be occupied with weekly bismuth injections) to place the patient on the standard or 26-week treatment schedule, the duration of which may be shortened to the extent of the mapharsen dosage before the reaction occurred (*e. g.,* if the patient received a total of 400 mg. mapharsen before the reaction, 1200 mg. additional should be given by injections twice weekly with bismuth added as in the standard schedule).

2. *Jaundice:* this is an uncommon complication and calls for discontinuance of intensive therapy. No instance of acute yellow atrophy has occurred although Rattner and Falk (1942) observed a case of severe hepatitis with other visceral damage (see below). For the treatment of this reaction, the patient may be given intravenous 10% dextrose solution, high carbohydrate-low fat diet, and injections of liver extract therapeutically. Intestinal elimination should be encouraged with saline catharsis.

3. *Blood dyscrasias* (especially purpura or bleeding from any part of the body): rarely encountered, but necessitating permanent discontinuance of all arsenotherapy. Treatment usually consists in blood transfusions.

4. *Exfoliative dermatitis:* rarely, if ever, encountered. Requires permanent discontinuance of all arsenotherapy. Symptomatic treatment, dextrose intravenously, and liver extract.

5. *Encephalopathy:* women are especially susceptible. This reaction may be manifested by severe headache, vertigo, tremor, fever, unusually severe nausea and vomiting, mental confusion, disorientation, and apathy; by single or repeated convulsive seizures, and by prolonged chorea. In serious instances hyperthermia usually supervenes and *death* may result. May occur on the 3th to 5th day of treatment, or not until the 6th or 7th day; rarely thereafter. Often preceded by headache of increasing severity (see above). There is no means of anticipating this reaction (Thomas, Wexler and Dattner, 1942). In mild cases, the suspicion of toxic encephalopathy should be checked by examination of the spinal fluid for cells, globulin or increased protein. If such tests are positive, further treatment with arsenical drugs should be abandoned. If the spinal fluid is normal, treatment may be resumed if the symptoms have completely disappeared and the temperature is normal.

Treatment of this serious reaction is of uncertain value but the prognosis is not as bad as is usually assumed (Chargin, 1940). Suggested procedures include (1) repeated drainage of spinal fluid (20 to 40 cc.) in repeated taps daily; (2) dehydration by use of intravenous 50% sucrose solution, 50 to 200 cc.; (3) sedation is of value in all cases. Where symptoms are mild, any of the barbiturates may be used by mouth. If convulsions occur, sodium amytal 0.24 gm. ($3\frac{3}{4}$ gr.) may be given intravenously or intramuscularly (this dose may be repeated every 2 to 3 hours for several doses if convulsions occur or the patient is restless; (4) adrenalin. Oxygen inhalations may also be given. Sodium thiosulfate is of no value (Chargin, 1940).

6. *Severe renal injury* (rare); Thomas and his colleagues (1943) have reported acute nephrosis in patients receiving short arsenical and prolonged fever treatment but no particular renal damage occurs in their patients treated with the multiple injection method (10- or 6-day). Rattner and Falk (1942) reported a severe case with acute glomerulonephritis, anuria, uremia, hepatitis, ileus and pericarditis in a patient treated by the 5-day method. This is *rare.*

Post-treatment Routine After 5 to 10 Day Intensive Therapy (to be carried out before discharge from hospital). (1) Complete physical examination. (2) Laboratory studies. (a) Titered blood serologic test for syphilis. (b) Complete urine analysis. (c) Complete blood count (hemoglobin, red blood cell and white blood cell count and differential). (d) Other laboratory procedures (icterus index, serum bilirubin, urobilinogen, non-protein nitrogen where indicated).

Outline of Proposed 12-Week Schedule of Modified Intensive Treatment (Eagle, 1943). Patients are to be treated with mapharsen (arsenoxide) 3 times weekly (Monday, Wednesday, and Friday; or Tuesday, Thursday, and Saturday) at the following dosage scale: less than 120 pounds (55 kg.), 50 mg.; 120 to 155 pounds (55 to 70 kg.), 60 mg.; greater than 155 pounds, 70 mg. Treatment is to continue for 12 weeks or to a total of 36 injections. Hospitalization is not necessary, and patients are to be treated on "duty status." Patients are to receive intramuscular injections of bismuth

subsalicylate (0.2 gm., equivalent to 0.13 gm. of metallic bismuth) once weekly throughout the course of mapharsen (arsenoxide) treatment, to a total of 12 injections.

Follow-up Observation After All Methods of Intensive Chemotherapy. 1. Patient should be reëxamined at monthly intervals for 6 months.

2. This reëxamination should include a complete physical examination with special attention to the mucous membranes of the mouth and throat; the genitals and the perianal region for easily overlooked evidences of infectious relapse.

3. Quantitative blood serologic tests for syphilis should be performed monthly for 6 months, and then at the 9th and 12th month. (The blood serologic reactions usually become negative at the 12th to 16th week after the start of treatment).

4. Examination of the spinal fluid should be done, if feasible, sometime between the 6th and 12th month.

5. The patient should not receive any further anti-syphilitic therapy, except as specifically set forth under "management of the unsatisfactory case."

Management of the Unsatisfactory Case. A patient who has become clinically "cured" and serologically negative and remained so until the 12th month of observation, and in whom the spinal fluid is negative, may be discharged from observation as a "satisfactory result." Should such a person return at a later date with a new dark-field positive lesion, this may be considered as a new infection and the patient may be re-treated in the original manner (Schoch, 1943; Moore, 1943; L. W. Shaffer, 1943). A case must be considered as unsatisfactory or a treatment failure, if: (a) There is definite objective evidence of infectious relapse, corroborated by a positive blood serologic reaction for syphilis, and if possible by positive dark-field examination. (b) There is incontrovertible evidence of serologic relapse without clinical relapse, *i. e.*, the patient's blood serologic reaction has dropped to negative or near negative and then to persistently strongly positive (this is best interpreted by a quantitative procedure). (c) Reagin fastness, *i. e.*, where the blood serologic reaction for syphilis has never reverted to negative but remains persistently positive (preferably determined by a constant titer of quantitative tests) for a 6 months period after treatment.

The unsatisfactory case (infectious relapse, serologic relapse, seroresistance, and the new infection) may be re-treated by intensive therapy except in the event of serious reaction from the original treatment. The results of intensive re-treatment of the unsatisfactory case have not been fully evaluated, but appear to be less satisfactory than original treatment.

Special Considerations Concerning Early Syphilis Treatment. *Criteria of Adequacy of Treatment for Syphilis.* The answer to this question depends fundamentally upon the definition of "adequacy." If by adequacy is meant the securing of a condition of non-infectiousness in an infectious case, one kind of answer will be appropriate; if adequacy is to be interpreted in terms of clinical or of radical cure, another answer will be appropriate; if adequacy means the placing of an infected individual at one or another type or stage of involvement in syphilis on asymptomatic status that will permit of full or limited service in the armed forces, still another answer is necessary. The subject is dealt with under each of these three heads briefly as follows:

Treatment of Non-infectiousness. The immediate infectiousness of surface lesions of syphilis is controlled in all but the rare treatment-resistant or arsenic-fast case, it will be recalled, by the first one, or at most two, injections of an effective trivalent arsenical, provided the dose is adequate (0.3 to 0.5 gm. arsphenamine 606; 0.4 to 0.6 gm. neoarsphenamine; 40 to 60 mg. mapharsen). The duration of this effect of 1 or 2 injections is not precisely known, but is estimated roughly as approximately 30 to 90 days. Failure to continue treatment does not necessarily, but may in a percentage of cases ranging from 0% to 64%, lead to infectious relapse.

A useful tabulation from the Cooperative Clinical Group and the University of Pennsylvania material is herewith presented:

Arsenical treatment alone, number of injections	Infectious relapse (%)	Additional heavy metal injections	Infectious relapse (%)
1– 4	64	20†	45.0
5– 9	14	20	9.0
10–19	..	20	4.0
20–29	..	20	3.6
28.8*	..	28.2 or more	0
30–40		"appropriate"	1.2

From this tabulation it will be apparent that the critical point at which sharp reduction in the probability of recurrent infectiousness takes place is between the 5th and 9th injections of the arsenical (14% relapse without and 9% with heavy metal); and that the so-called 20–20 standard, often quoted as adequate for treatment to non-infectiousness, reduces the risk of infectious relapse to 4%, beyond which a slow reduction to 0% to 1.2% is secured by prolonging treatment beyond 20 arsenical injections with 30 or more injections of heavy metal.

Heavy metal, in the statistical table presented above, is taken to represent 0.2 gm. of an insoluble bismuth salt of not less than 57% metallic content, or 1 week of mercurial inunctions, or its intramuscular equivalent in a water-soluble or insoluble mercurial salt.

It will presently be apparent therefore that the best treatment to secure non-infectiousness is practically identical with the optimum treatment for the securing of "satisfactory results" or "cure."

The Influence of the Development of Secondaries on Relapse. An interesting and seemingly paradoxical situation was revealed in the comparison of serological with clinical relapse under treatment—a relation of particular importance because it might well form the basis for polemic discussion. The stage of syphilis at which treatment is begun influences the incidence of mucocutaneous relapse in a different way from that in which it affects all other forms of relapse. The first Cooperative Clinical Group survey of mucocutaneous relapse as such[44] indicated that it occurs in 10% of patients beginning treatment in the seronegative primary stage; 8.6% of those beginning treatment in the seropositive primary stage; and only 4.2% in those who began treatment after their secondaries had fully developed.‡ Relapse incidence of the mucocutaneous type was therefore markedly less if the patient was allowed to develop his full cutaneous secondary reaction to the disease, the difference amounting to as much as 58% reduction in probability as the patient passed from a seronegative primary to the florid secondary phase. On the other hand, the existence of a distinct relapsing type was foreshadowed by the fact that patients who began treatment with late or recurrent secondaries relapsed in 22.3% of cases. Serologic relapse, on the other hand, occurred in 12% of patients whose treatment was begun in seronegative primary syphilis; 15.1% under the same circumstances in early secondary syphilis (1st year); and 20% if treatment was not begun until delayed secondaries after the 1st year. It appears, therefore, that to begin the treatment of a patient in the sero-

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* University of Pennsylvania figures; all others are C. C. G.
† One week of mercurial inunctions equals 1 injection.
‡ The percentages estimated on the basis of 3244 cases observed and treated for six months or over were seronegative primary 16.4%, seropositive primary 20.2%, secondary (first year) 9.5%, secondary delayed 9.2%. The principle illustrated is the same in both.

negative stage of primary syphilis, while it has already been shown definitely to increase the prospect of complete cure, nonetheless subjects him to a definite slight risk of mucocutaneous recurrence and therefore of more prolonged infectiousness. The probable explanation, of course, is that the skin and mucous membranes have never been given the opportunity to develop what might be thought of as a local tissue immunity by full reaction to the disease.

It must, of course, be appreciated that the reduced incidence of relapse and progression in patients who have had secondaries arises simply from the fact that in reaching that stage they have automatically, so to speak, set behind them that much of the life history of the disease. It must, too, remain for further study to decide whether the increased risk of infectious recurrence after early treatment justifies postponement until the patient has developed secondaries. At the present time the higher proportion of curative results seems to justify immediate treatment rather than postponement. The increased risk of infectiousness through recurrence can hardly be greater than the risk of infectiousness represented by a patient who is allowed to live at large in the community without benefit of the arsphenamines until his secondary eruption has fully developed. In any event, the application of such a principle demands universal hospitalization for the patient between the primary stage and the full development of secondaries, an obvious impracticability at this time. Until the proponents of postponement (as for example, Bernard) can advance indubitable evidence that there is other than merely mucocutaneous protective value in permitting a patient to go on to secondaries, the postponement of treatment until secondaries develop is not only against the interests of the public health but against that of the individual patient who above all things, desires the greatest possibility of personal cure.

Jadassohn, from an international questionnaire,[24] has reported that the effect of arsphenamine in controlling the infectiousness of syphilis had led to an estimated reduction in incidence of new cases of the disease of 75% to 80% in Belgium, Sweden, and Holland; 60% in Finland; 50% in Denmark; 50% to 80% in Switzerland; 30% to 60% in Italy and Czechoslovakia; and 25% in Norway.

Rules for Preventing Infectious Relapse. The prevention of infectious recurrence and the reduction of relapse to the lowest possible terms requires of the practitioner, then, an unhesitating acceptance of the following rules: (1) The concept of abortive cure by short courses should be abandoned, no matter how early the patient may come under treatment. (2) Not less than 20 injections of an arsphenamine, and more if possible, preferably in 1 or 2 courses, and an equivalent amount of heavy metal without rest intervals, should be given in an early case to control infectiousness. (3) Treatment should be continuous rather than intermittent or intensive, there being no time, at least within the first year or more, that the patient is not under the influence of one or another effective mode of treatment for syphilis with an arsphenamine or heavy metal. (4) Treatment should be massed well to the fore—that is, within the first 3 months, for this is the period in which mass as distinguished from prolongation, reaches its greatest effectiveness in preventing relapse. (*Cf.* Massive dose arsenotherapy.)

Stokes, Miller and Beerman[25] in their study of bismuth arsphenamine sulfonate observed a similar phenomenon. The proportion of relapse in continuous treated cases was 9.1% and in those allowed rest intervals 14.3%. Of the continuously treated cases 60% had comparatively little treatment (20 injections or less) while

86% of the intermittently treated patients who had the higher incidence of relapse had had comparatively heavy courses of 21 injections or more (40% had over 40 injections). It appeared that a small amount of treatment continuously applied yielded fewer relapses of all kinds than a larger amount with rest periods or lapses.

With so much emphasis placed on the seriousness of lapse in the promotion of infectious recurrence, it is proper to emphasize as the 5th rule for the physician, his responsibility in educating his patient and in holding him to a sufficiently prolonged course and in utilizing follow-up assistance if and when it is available. (6) He should understand, too, that infectious relapse is detected by actual physical examination with special emphasis on the mouth, anus, and genitalia rather than by serologic tests. One should examine especially the lips, penis, scrotum and vulva. (7) Positive serologic tests may warn of infectious relapse and confirm the diagnosis, but since they cannot be frequently applied, physical examination and instruction of the patient himself in the recognition of infectious lesions are the more important approaches. (8) Serologic tests and stripped physical examinations, to be of value in detecting relapse, should, if anything, be more frequently made after treatment is completed and the patient is put on observation than during treatment itself. The opposite is common practice, and this applies especially to the first 2 or 3 years of the disease. (9) Negative serologic reactions, as has been repeatedly emphasized, are not proof of non-infectiousness, immediate or future. A negative serologic reaction should not deceive the physician or patient into relaxing precautions. (10) Treatment and time are the chief preventives of infectiousness. (11) Since potentially infectious relapses occur overwhelmingly in the first 2 years of early syphilis, sexual relations and intimate contact without absolute protection should be allowed *only while the patient is under actual arsenical treatment.* The duration of non-infectiousness when treatment is stopped before the 12th injection of arsphenamine may not, apparently, exceed 1 month.

Adequacy With Respect to "Cure" or "Satisfactory Results." Information on this subject is based on case material observed for not less than 2, and upward to 20, years since the onset of the infection or the institution of treatment. Material of less than 2 years of observational control is fundamentally weak in its demonstration of the possibility of relapse, since the first 2 years of infection are overwhelmingly those of relapse predisposition. On adequacy in the sense of "satisfactory results," 5 groups of data will be quoted: (a) Cooperative Clinical Group results in the treatment of early syphilis by a continuous alternating use of arsenical and heavy metal without rest period, through 65 weeks of treatment observation; (b) Padget's[36] Johns Hopkins Hospital Syphilis Clinic report on 551 patients completely reëxamined 5 years or more after the termination of their original treatment for early syphilis; (c) optimal treatment for early syphilis, 1 to 20 years observation;[12] (d) a shortened 20-week system, Hood[23] reporting on Johns Hopkins Hospital material; (e) the 5-day intensive intravenous drip arsenotherapy of syphilis (without the use of heavy metal), Leifer, Chargin and Hyman (1941) and Elliott, Baehr, Shaffer, Usher and Lough (1941).[16]

It is not possible at this time to offer more than speculative estimates on 10-day multiple syringe and 10- to 12-week intensive mapharsen-bismuth[16] systems which are under study.

The Cooperative Clinical Group's standard treatment system experience indicates that for satisfactory results, treatment must be continuous and not inter-

mittent or irregular, and must combine the alternate use of an effective arsenical (mapharsen is not represented in this material) and a bismuth. Striking reductions in effectiveness with occurrence of infectious relapse, progression of syphilitic manifestations, serologic relapse and seroresistance occur in all phases of early syphilis in which intermittence or irregularity is allowed to occur. Disregarding the precise system of administration, the highest proportion of satisfactory results in seronegative primary syphilis was obtained with 10 to 19 injections of arsphenamine with accompanying heavy metal; in seropositive primary syphilis, with 25 to 35 injections; in early secondary syphilis (seen in the 1st year) 20 to 29 injections. Higher rather than lower dosage of the arsphenamine is recommended. Failure to secure a satisfactory result by 20 injections or less may be met by 10 additional injections, plus heavy metal, which may double the proportion of unsatisfactory outcomes reclaimed. The irreducible margin of failure in the treatment of early syphilis by older standards ranges from 4% to 27%, depending on method, stage at which treatment is begun, adequacy of treatment during the first 2 years of infection.

The Johns Hopkins Syphilis Clinic material[36] is particularly valuable because of the length of observation (over 10 years in half of the patients), and shows clearly the importance to adequacy of the treatment results of the stage at which treatment is begun (82% cure in seronegative primary syphilis, 68.8% in secondary syphilis, 58.7% in early latent syphilis). The poorest results, as in the Cooperative Clinical Group series were observed among patients whose treatment was begun in the seropositive primary stage. Cure was obtained by 83.4% of the patients whose treatment during the first 6 months was by a continuous system, and is increased to 90.4% if treatment during the next 6 months was likewise continuous. It was shown that the final or "adequate outcome" depended in a directly quantitative fashion not only on the number of doses of the arsphenamine received, but also inversely, upon the time span during which it was given. In other words, the more injections in the shorter time, the better the results. The development of early or intermediate relapse was found to be of grave prognostic significance.

Cannon found in a series of some 600 patients treated with 3 standard arsphenamines, that arsphenamine 606 was incontestably superior to neoarsphenamine or silver arsphenamine, and that 1 year of regular and continuous treatment with the arsenical injections closely spaced (2- and 3-day intervals in the first 3 to 5 weeks and at intervals of not less than 1 week thereafter) gave the highest proportion of satisfactory results. The difference between seronegative primary, seropositive primary and secondary syphilis was not more than 6%.

The 20–20 Arsenical-Bismuth Simultaneous Injection Course (Hood). This shortened system, not comparable because of longer intervals (weekly) with the 26-week system of Circular Letter No. 74, utilizes weekly injections of mapharsen and simultaneous weekly intramuscular injections of an oil-suspended bismuth salt. The maximum period of observation (33 months) was only sufficient to indicate that the proportion of unsatisfactory results in the form of seroresistance, serorelapse, clinical relapse and involvement of the central nervous system, amounting to 13.6% of the observed series, was approximately that of unsatisfactory results obtained in early syphilis treated with other arsenical drugs and treatment systems. If confirmed by longer observation, such a treatment system should show how little rather than how much treatment is necessary to produce the average or so-called "standard" results which are so strikingly uniform throughout the entire range from 5-day intravenous drip to 65-week continuous combined therapy.

Massive Dose Arsenotherapy ("5-Day Drip"). The 2 series, Leifer *et al.*, and Elliott *et al.*, the former with of course the longer series of observed cases, illustrates the following principles regarding adequacy: (a) Curative results can be obtained with a trivalent arsenical alone (neoarsphenamine, mapharsen). (b) Of the two, mapharsen because of its low reactivity is the drug of choice, and 1200 mg. administered in 5 days, the optimum dose. (c) In seronegative primary syphilis, 90 to 100% pursue a satisfactory and uneventful course; without reference to type of drug or stage of disease, an aggregate of 81% secured a satisfactory result in one 5-day course, and one re-treatment in 15 cases raised the result to approximately

88% for the entire series (Leifer *et al.*). Elliott and co-workers estimated their curative results at at least 85% of all cases with early syphilis.

Adequacy of Treatment From the Standpoint of Service in the Armed Forces. A tentative basis for evaluation proposed for admission of registrants with syphilis to the United States Army is as follows:

Registrants with (1) confirmed positive serologic tests for syphilis and no clinical manifestations of the disease; or (2) with convincing histories of a trustworthy diagnosis of syphilis; or (3) of treatment for the disease on serologic or clinical grounds even though such evidence may possibly have been inadequate, may be considered for unlimited military service: (a) Provided that a negative spinal fluid since treatment was begun has been reported from a trustworthy source; and (b) provided that in infections estimated to be of less than 4 years duration, at least 30 to 40 arsenical and 40 to 60 insoluble bismuth injections or its equivalent with a minimum total of 75 injections have been given, with approximate continuity (no rest periods or lapses) during the first 30 weeks of treatment; and (c) provided that except as further qualified below in infections estimated to be over 4 years duration, at least 20 arsenical injections or its equivalent with a minimum total of 60 injections have been given in alternating courses; rest periods between consecutive courses not exceeding 8 weeks, being allowable.

Evidence of duration of the infection shall be weighed by the examiner with due regard for the age, general venereal history and medical guidance of the registrant.

In infections of *unknown duration* it shall be presumed for classification purposes that those of registrants under 26 years of age are of less than 4 years duration, and over 26 years of age, of more than 4 years duration.

In congenital infections and in acquired infections of more than 10 years known duration, in which no clinical progression occurred since treatment was begun; and in which a normal spinal fluid has been recorded at some time after treatment was begun and negative physical examination is recorded not less than 2 years after treatment was terminated, the infection shall be regarded as "quiescent," and the registrant eligible for unlimited military service; provided the treatment in question shall have included 20 arsenical and 20 heavy metal injections.

For the determination of treatment, the signed statements of acceptable treatment sources administering it with total number of doses of each drug and approximate calendar dates of administration and available laboratory and clinical data shall be required as evidence.

The Prognostic Significance of Secondary and Serologic Relapse. The following principles, based in the main upon the groups of material cited in connection with the criteria of adequacy of treatment for syphilis, are widely accepted. Early evidence of potentially unfavorable or relapsing course in an early syphilitic infection can be found in (a) failure of the primary or secondary lesions to heal under an arsenical therapy; (b) continued presence of *Sp. pallida* in the lesions after the employment of a known effective trivalent arsenical (these 2 groups constitute treatment resistance in syphilis;[a] (c) prematurely early reversal of a positive serologic reaction on the blood to negative (4th to 7th week in seropositive primary or secondary syphilis); (d) failure of a positive serologic reaction on the blood to reverse to negative after the 16th week (in the intensive or 5-day drip system reversal is ordinarily expected by quantitative tests between the 10th and 18th weeks after the institution of treatment but late secondaries may not reverse for many months even though "cured").

Cooperative Clinical Group results[13] (observation period too short) showed a relapse expectancy of 19.7% including all forms, of which, when observed for more than 6 months, 12.1% was mucocutaneous, 3.4% asymptomatic neurosyphilis, 4.1% symptomatic neurosyphilis, and 0.9% cardiovascular syphilis.

The unfavorable prognostic significance of early and intermediate relapse was well brought out in Padget's series in which "cure" was achieved in 73.2% of 456 patients in whom no relapse was observed, whereas only 28.2% of those sustaining an intermediate relapse achieved "cure". Persistent seropositive reactions on the blood, however, occurred in 16% of those who sustained no relapse, and in 10.3% of those who underwent intermediate relapse. Late benign syphilis developed 8 times as frequently in relapsers as in non-relapsers, cardiovascular syphilis

3.5 times as frequently; neurosyphilis 6 times as frequently; multiple late manifestations 7.5 times as frequently in relapsers as in non-relapsers. The occurrence of weak positive serologic reactions on the blood appearing in the course of a series of negatives in treated early syphilis have been emphasized as of relapse significance by certain authors.

Significance of Seropositivity After Treatment Which Was Begun During Early Syphilis. Broadly speaking, Padget's experience indicated that a residue of 14.9% persistent serologic positiveness would appear in a series of early syphilitics on whom the satisfactory results he described had been secured. In these cases there would be no manifestations such as abnormal spinal fluid, cardiovascular disease, visceral disease and so forth to accompany the persistent seropositiveness. The inclination would be, therefore, to rate it in these cases as without significance. In general, however, persistence of a positive serologic reaction on the blood of early syphilitics under treatment by the older standard continuous systems was an indication of presence of asymptomatic neurosyphilis, and called for an examination of the spinal fluid immediately.[25,48] The more intensive foreshortened treatment systems seem so materially to have reduced the likelihood of the occurrence of asymptomatic neurosyphilis that the neurosyphilitic significance of persistent seropositivity will probably be greatly reduced by their use. In addition, to asymptomatic neurosyphilis, syphilis of the cardiovascular system, often coming to recognition 5 or more years after the cessation of treatment, may be included in the prognostic significance of seropositiveness of a persistent type in early syphilis.

The Prevention of Cardiovascular Syphilis. This is still the *terra incognita* of modern syphilology and the studies thus far summarized have thrown relatively little light upon it. Langer[26] and others have attributed the increase in the incidence of aortitis since 1912 to the use of arsphenamine in the treatment of syphilis, but our experience with this drug in early syphilis fails to substantiate this belief, the incidence of recognizable aortic lesions not increasing materially in the period studied. It is, of course, true that our study does not extend forward into the period of maximum recognition of this form of syphilis. Moore, Danglade and Reisinger[29] in considering Langer's contention, believed that the apparent increase coincident with the use of arsphenamine in treatment is due rather to more accurate pathologic study with increasing knowledge of microscopic appearance of aortic syphilis. Progression of cardiovascular syphilis in spite of various methods of treatment occurred in 0.8% to 1.2% of our patients. Warthin's[49] observation, which placed the incidence of aortic syphilis in syphilitic adults between 1909 and 1919 at 97.6%, and between 1919 and 1929 at 86.3%, further supports the view that arsphenamine is not responsible for the apparently increasing incidence observed by Langer.

Moore and Padget[32] in their analysis of seroresistant syphilis (early) emphasize the seriousness of seroresistance in early syphilis and its relatively lesser significance in late syphilis. Twenty-three per cent of their seroresistant group sustained infectious relapse as against 5% who secured prompt serologic reversal. Neurosyphilis occurs in 31% of the seroresistant cases, but in only 18% of those who sustain prompt reversal.

REFERENCES

(1.) Almkvist, J.: (a) Acta dermato-venereol., 1, 97, 1920; (b) Arch. f. dermat. u. syph., 150, 179, 1926. (2.) Becker, S. W. (cited by Stokes, J. H.): Modern Clinical Syphilology, 1st ed., Philadelphia, W. B. Saunders Company, 1926. (3.) Beerman, H.

et al. (*a*) Am. J. Syph., Gonor. and Ven. Dis., **20**, 165 and 296, 1936; (*b*) Publication No. 6, Am. Assn. for Advancement of Science, p. 77, 1938; (*c*) **Beerman, H.,** and **Severac, M.:** J. Invest. Dermat., **5,** 269, 1942; (*d*) **Beerman, H., Ingraham, N. R., Jr.,** and **Pariser, H.:** Am. J. Syph., Gonor. and Ven. Dis., **27,** 460, 1943. (4.) **Bering, F.:** Dermat. Wchnschr., **73,** 900, 1921. (5.) **Bernard, R.:** Bruxelles méd., **8,** 1602, 1928. (6.) **Boak, R. A., Carpenter, C. M.,** and **Warren, S. L.** (cited by **Simpson, W. M., Kendell, H. W.,** and **Rose, D. L.**): Supplement No. 16 to Ven. Dis. Inform., 1942. (7.) **Boas, H.:** (*a*) Acta dermato-venereol., **3,** 559, 1922; (*b*) Hospitalstid., **65,** 153, 1923. (8.) British Scandinavian (League of Nations) System): J. Am. Med. Assn., **104,** 1329, 1935. (9.) **Bruck, W.:** München. med. Wchnschr., **69,** 1624, 1922. (10.) **Bruns, A.:** Dermat. Wchnschr., **78,** 661, 1924. (11.) **Bruusgaard, E.:** Norsk. Mag. f. Lægevidensk., **89,** 1222, 1928. (12.) **Cannon, A. B.:** Am. J. Syph., Gonor. and Ven. Dis., **21,** 155, 1937. (13) Cooperative Clinical Group:

    Stokes, J. H., Cole, H. N., Moore, J. E., O'Leary, P. A., Parran, T., Jr., and Wile, U. J.: Ven. Dis. Inform., **12,** 55, 1931.

    Clark, T., Parran, T., Jr., Cole, H N., Moore, J. E., O'Leary, P. A., Stokes, J. H., and Wile, U. J.: Ven- Dis. Inform., **13,** 135, 165, 207, 253, 1932.

    Moore, J. E., Cole, H. N., O'Leary, P. A., Stokes, J. H., Wile, U. J., Clark, T., Parran, T., Jr., and Usilton, L. J.: Ven. Dis. Inform., **13,** 317, 351, 371, 389, 407, 1932; and **14,** 1, 1933.

    Stokes, J. H., Usilton, L. J., Cole, H. N., Moore, J. E., O'Leary, P. A., Wile, U. J., Parran, T., Jr., and McMullen, J.: Am. J. Med. Sci., **188,** 660, 669, 678, 1934.

    O'Leary, P. A., Cole, H. N., Moore, J. E., Stokes, J. H., Wile, U. J., Parran, T., Jr., Vonderlehr, R. A., and Usilton, L. J.: Ven. Dis. Inform., **18,** 45, 1937.

(14.) **Eagle, H.,** and **Hogan, R. B.:** J. Clin. Invest., **21,** 634, 1942. (15) **Eicke, H :** Deutsch. med. Wchnschr., **47,** 412, 1921. (16.) Foreshortened Intensive Methods. (These references are arranged chronologically.)

    Hirshfeld, S., Hyman, H. T., and Wanger, J. J.: Arch. Int. Med., **47,** 259, 1931.

    Hyman, H. T., and Hirshfeld, S : (*a*) J. Am. Med. Assn., **100,** 305, 1933; (*b*) Ibid., **96,** 1221, 1931.

    Hyman, H. T., and Touroff, A. S. W.: Ibid., **104,** 446, 1935.

    Chargin, L., Leifer, W., and Hyman, H. T.: J. Am. Med. Assn., **104,** 878, 1935.

    Tzanck, A., Duperrat, and Lewi, S : Bull. et mém. Soc. méd. d. hôp. de Paris, **54,** 268, 1938; Bull. Soc. franc. de dermat. et syph., **45,** 404, 1938, also **44,** 2028, 1937.

    Tzanck, A.: Bull. Acad. de méd., **119,** 257, 1938; Bull. Soc. franc. de dermat. et syph., **45,** 587, 1938.

    Hyman, H. T., Chargin, L., and Leifer, W.: Am. J. Med. Sci., **197,** 480, 1939.

    Editorial: Am. J. Syph., Gonor. and Ven. Dis., **23,** 797, 1939.

    Hyman, H. T., Chargin, L., and Leifer, W.: Am. J. Syph., Gonor. and Ven. Dis., **23,** 685, 1939.

    Hyman, H. T., Chargin, L , Rice, J. L., and Leifer, W.: J. Am. Med. Assn., **113,** 1208, 1939.

    Clark, R. E.: J. Wayne Univ. College of Med., **3,** 19, 1940.

    Queries and Minor Notes: Jour. Am. Med. Assn., **114,** 345, 1940.

    Corres.: Lancet, **1,** 896, 1940.

    Editorial: Med. Rec., **151,** 297, 1940.

    Corres.: Canad. Med. Assn. J., **43,** 184, 1940.

    Raulston, B. O., and Magnuson, H. J.: Trans. Assn. Am. Phys., **55,** 255, 1940.

    Brayton, J. R., and Winebrenner, J. D.: J. Indiana Med. Assn., **33,** 368, 1940.

    Baehr, G.: Arch. Dermat. and Syph., **42,** 239, 1940.

    Leifer, W.: Arch. Dermat. and Syph., **42,** 245, 1940.

    Chargin, L.: Arch. Dermat. and Syph., **42,** 248, 1940.

    Hyman, H. T.: Arch. Dermat. and Syph., **42,** 253, 1940.

    Webster, B.: Arch. Dermat. and Syph., **42,** 264, 1940.

    Thomas, E. W.: Arch. Dermat. and Syph., **42,** 267, 1940.

    Sobotka, H., Mann, W., and Feldbau, E.: Arch. Dermat. and Syph., **42,** 270, 1940.

    Current Comment: J. Am. Med. Assn., **115,** 863, 1940.

    Simons, R. D. G. P.: Geneesk. tijdschr. v. Nederl.-Indië, **80,** 2245, 1940.

    Mahoney, J. R.: Arch. Dermat. and Syph., **42,** 262, 1940.

    Discussion: Discussion of papers by Drs. Baehr, Leifer, Chargin, Hyman, Mahoney, Webster, Thomas and Sobotka, Mann and Feldbau, Arch. Dermat. and Syph., **42,** 276, 1940.

    Rice, J. L.: Arch. Dermat. and Syph., **42,** 283, 1940.

    Editorial: Internat. Med. Digest., **37,** 310, 1940.

    Hoffmann, E.: München. med. Wchnschr., **87,** 1264, 1940; comment by Stühmer, **87,** 1450, 1940.

Takesita, S.: Hihuto-Hitunyo (Abst. Sect.), 8, 40, 1940.
Clarke, W.: Bull. Vancouver Med. Assn., 16, 323, 1940.
Howkins, J. S.: J. Med. Assn. Georgia, 29, 452, 1940.
Council Report: J. Am. Med. Assn., 115, 857, 1940.
Editorial: Massive Arsenotherapy in Syphilis, Brit. Med. J., 2, 911, 1940.
Nelson, L. M.: Staff Meet. Bull., Hospitals of the Univ. of Minnesota, 12, 26S, 1941.
Chargin, L., and Leifer, W.: Arch. Dermat. and Syph., 43, 419, 1941.
Baehr, G.: Am. J. Pub. Health, 31, 176, 1941.
Cabrera, E.: Rev. Fac. de med., Bogota, 9, 481, 1941.
Hyman, H. T.: Bull. New York Acad. Med., 17, 135, 1941.
Magnuson, H. J., and Raulston, B. O.: Ven. Dis. Inform., 22, 157, 1941.
Gordon, H.: South African Med. J., 15, 165, 1941.
Gabby, W. H., Neilson, A. A., and Maxwell, R. W.: Proc., J. Bact., 41, 785, 1941.
Rattner, H.: Illinois Health Messenger, 13, 44, 1941.
Magnuson, H. J., and Raulston, B. O.: Ann. Int. Med., 14, 2199, 1941.
Thomas, E. W., and Wexler, G.: Am. J. Pub. Health, 31, 545, 1941.
Shaffer, L. W.: J. Michigan Med. Soc., 40, 529, 1941.
Schoch, A., and Alexander, L. J.: Am. J. Syph., 25, 607, 1941.
Elliott, D. C., Baehr, G., Shaffer, L. W., Usher, G. S , and Lough, S. A.: J. Am. Med. Assn., 117, 1160, 1941.
Leifer, W., Chargin, L., and Hyman, H. T.: J. Am. Med. Assn., 117, 1154, 1941.
Epstein, N. N.: California and Western Med., 55, 24S, 1941.
Scholtz, J. R.: Ven. Dis. Bull. I, California Dept. Pub. Health, No. 7, p. 3, 1941.
Morales Beltrami, R.: Rev. med. de Chile, 69, 140, 1941.
Leifer, W.: Med. Clin. North America, 25, 775, 1941.
Axelrod, S. J.: Am. J. Nursing, 41, 1039, 1941.
Weinstein, M., and Barria, C.: Rev. med. de Chile, 69, 562, 1941.
O'Malley, C. K.: South African Med. J., 15, 343, 1941.
Trautman, J. A.: Hosp. News, 8, 12, 1941.
Barletta, J. L.: Dia. med., 13, 1193, 1941.
Bowman, G. W., and Sheehan, F. G.: J. Indiana Med. Assn., 34, 665, 1941.
Kolmer, J. A., and Rule, A. M.: Arch. Dermat. and Syph., 44, 1055, 1941.
Magnuson, H. J., and Raulston, B. D.: Ven. Dis. Inform., 22, 431, 1941.
Prats, G. F., Infante Varas, L., and Haraszti, E.: Rev. med. de Chile, 69, 733, 1941.
Infante Varas, L.: Rev. med. de Chile, 69, 729, 1941.
Dussert, E.: Rev. med. de Chile, 69, 743, 1941.
Bryan, J.: Geneesk. tijdschr. v. Nederl.-Indië, 81, 2350, 1941.
Levin, I. M., Hoffman, S. J., and Koransky, D.: Am. J. Dis. Child., 63, 201, 1942.
Rattner, H.: Illinois Med. J., 81, 29, 1942.
Berry, N. E.: Am. J. Syph., 26, 204, 1942.
Young, W. A., and Gordon, S : East African Med. J., 19, 123, 1942.
Eagle, H., and Hogan, R. B.: Science, 95, 360, 1942.
Usher, B., and Hill, A. E.: Canad. Med. Assn. J., 46, 342, 1942.
Rattner, H., and Falk, A. B.: J. Am. Med. Assn., 118, 136S, 1942.
Prunes, L., and Hevia, P. H.: Arch. Dermat. and Syph., 45, 894, 1942.
Editorial: J. Am. Med. Assn., 120, 4S, 1942.
Simpson, W. M., Kendell, H. W., and Rose, D. L.: Ven. Dis. Inform. (Suppl. 16), p. 41, 1942.
Avery, W. H.: Canad. Pub. Health J., 33, 1, 1942.
Stephenson, C. S., Chambers, W. M., and Anderson, L. T.: U. S. Naval Med. Bull., 40, 215, 1942.
Hoffmann, E.: Dia. med., 14, 102, 1942.
King, A. C.: Texas State J. Med., 37, 726, 1942.
Sadusk, J. F., Jr., and Shaffer, T. E.: Yale J. Biol. and Med., 14, 365, 1942.
Marin, A.: Canad. Med. Assn. J., 46, 334, 1942.
Kaplan, B. I.: Arch. Dermat. and Syph., 45, 941, 1942.
Prats, G. F., Infante Varas, L., and Haraszti, E.: Arch. Dermat. and Syph., 45, 885, 1942.
Prats, G. F., Infante Varas, L., Simon, K. T., and Harazsti, E.: Rev. Argent. dermatosif., 26, 65, 1942.
Body, E. F., Haraszti, E., and Giacamon, J.: Rev. Argent. dermatosif., 26, 92, 1942.
Brun, J. F., Ramirez, D., and Román, A.: Rev. méd. veracruzana, 22, 3691, 1942.
Goodman, H.: Urol. and Cutan. Rev., 46, 379, 1942.
Sadusk, J. F., Jr., Craige, B., Jr., Brookens, N., Poole, A. K., and Strauss, M. J.: Yale J. Biol. and Med., 14, 333, 1942.
Marin, A.: L'Union méd. du Canada, 71, 342, 1942.
Schoch, A. G., and Alexander, L. J.: Arch. Dermat. and Syph., 46, 12S, 1942.

Wallis, S. R.: Hawaii Med. J., 1, 363, 1942.

Editorial: Am. J. Syph., Gonor. and Ven. Dis., 26, 510, 1942.

Geiger, A. J., Craige, B., Jr., and Sadusk, J. F., Jr.: Yale J. Biol. and Med., 14, 357, 1942.

Falk, A. B., and Rattner, H.: Arch. Dermat. and Syph., 46, 283, 1942.

Thomas, E. W., Wexler, G., and Dattner, B.: Am. J. Syph., Gonor. and Ven. Dis., 26, 529, 1942.

Pelzman, I. A., and Greenwald, E.: Am. J. Syph., Gonor. and Ven. Dis., 26, 637, 1942.

Nelson, E. E.: Internat. Med. Digest., 41, 182, 1942.

Levin, E. A., and Keddie, F.: J. Am. Med. Assn., 118, 368, 1942.

Roemer, M. I.: J. Med. Soc. New Jersey, 39, 498, 1942.

Siegel, J., Goldstein, D. H., and Goldwater, L. J.: Arch. Dermat. and Syph., 46, 783, 1942.

Levin, I. M., Hoffman, S. J., Koransky, D. S., Richter, I. B., and Gumbiner: J. Am. Med. Assn., 120, 1373, 1942.

Kvittingen, J.: Brit. Med. J., 1, 69, 1943.

Arnold, H. L., Jr.: Proc. Staff Meet. Clinic Honolulu, 9, 1, 1943.

Eagle, H., and Hogan, R. B.: Ven. Dis. Inform., 24, 33, 69 and 159, 1943.

Schoch, A. G., and Alexander, L. J.: Am. J. Syph., Gonor. and Ven. Dis., 27, 15, 1943.

Editorial: (J. E. M.) Ibid., p. 108.

Shaffer, L. W.: Ven. Dis. Inform., 24, 108, 1943; Ibid., p. 113.

Schwind, J. L.: Proc. Soc. Exper. Biol. and Med., 52, 128, 1943.

Thomas, E. W., and Wexler, G.: Arch. Dermat. and Syph., 47, 563, 1943.

Hood, B. J.: Am. J. Syph., Gonor. and Ven. Dis., 27, 267, 1943.

Thomas, E. W., Wexler, G., Schur, M., and Goldring, W., with technical assistance of Eggleston, N.: J. Am. Med. Assn., 122, 807, 1943.

Bowman, G. W., and Huber, C. P.: Monthly Bull. Indiana State Board of Health, 46, 86, 1943.

Rattner, H.: J. Am. Med. Assn., 122, 986, 1943.

Harris, H. L., and Sorensen, R. M.: Iowa State Med. J., 33, 254, 1943.

(17.) Gennerich, W.: Die Syphilis des Zentralnervensystems, Berlin, Julius Springer, 1922. (18.) Hahn, R. D.: Am. J. Syph., Gonor. and Ven. Dis., 25, 659, 1941. (19.) Harrison, L. W.: (a) Practitioner, 126, 193, 1931; (b) Med. Research Council, Spec. Report, No. 132, 1929; (c) The Diagnosis and Treatment of Venereal Diseases in General Practice, Oxford, p. 427, 1931. (20.) Haxthausen, H.: Ugesk. f. Læger, 81, 217, 1919. (21.) Hoffmann, E.: Therap. d. Gegenw., 63, 11, 1922. (22.) Hoffmann, E., and Mergelsberg, O.: Dermat. Ztschr., 35, 1, 1921. (23.) Hood, B.: Am. J. Syph., Gonor. and Ven. Dis., 27, 267, 1943. (24.) Jadassohn, J.: (a) Ztschr. f. ärztl. Fortbild., 23, 749, 1926; (b) Klin. Wchnschr., 1, 1193, 1243, 1922; (c) Ibid., 5, 2248, 1926. (25.) Kemp, J. E., and Menninger, W. C.: Bull. Johns Hopkins Hosp., 58, 24, 1936. (26.) Langer, E.: München. med. Wchnschr., 73, 1782, 1926. (27.) Leredde, E.: (a) La sterilisation de la syphilis, Paris, A. Maloine, 1912; (b) Paris méd., 7, 153, 1917. (28.) Martenstein, H.: Quart. Bull. Health Organ, League of Nations, 4, 129, 1935; see also J. Am. Med. Assn., 104, 1329, 1935. (29.) Moore, J. E., Danglade, J. H., and Reisinger, J. C.: Arch. Int. Med., 49, 753, 1932. (30.) Moore, J. E., and Keidel, A.: Bull. Johns Hopkins Hospital, 39, 1, 1926. (31.) Moore, J. E., and Kemp, J. E.: Bull. Johns Hopkins Hosp., 39, 16, 36, 1926. (32.) Moore, J. E., and Padget, P.: J. Am. Med. Assn., 110, 96, 1938. (33.) Müllern-Aspegren: Acta Dermat-Vener., 3, 572, 1922. (34.) Mutschler, R.: Arch. f. derm. u. syph., 147, 107, 1924.

(35.) Ormsby, C. S.: J. Am. Med. Assn., 56, 504, 1911, and 75, 1, 1920. (36.) Padget, P.: Am. J. Syph., Gonor. and Ven. Dis., 24, 692, 1940. (37.) Pollitzer, S.: J. Cutan. Dis., 34, 633, 1916. (38.) Rasch, C.: Nordisk. Bibliotek for Therapi, p. 10, 1922. (39.) Riecke: München. med. Wchnschr., 66, 969, 1919. (40.) Rost: Arch. f. Derm. u. Syph., 138, 89, 1922. (41.) Satke, V.: Dermat. Ztschr., 39, 349, 1923. (42.) Silberstein, S.: Arch. f. derm. u. syph., 143, 334, 1923. (43.) Stokes, J. H.: (a) Ven. Dis. Inform., 17, 315, 1936; (b) J. Connecticut State Med., 2, 172, 1938; (c) J. Am. Med. Assn., 120, 1093, 1942. (44.) Stokes, J. E., Besancon, J. H., and Schoch, A. G.: J. Am. Med. Assn., 96, 344, 1931. (45.) Stokes, J. H., Miller, T. H., and Beerman, H.: Arch. Derm. and Syph., 23, 624, 1931. (46.) Stokes, J. H., and Usilton, L. J.: Ven. Dis. Inform., 18, 66, 1937; Arch. Dermat. and Syph., 35, 377, 1937. (47.) Ullmann, K.: Wien. Klin. Wchnschr., 35, 455, 479, 502, 951, 1922. (48.) Vonderlehr, R. A., and Usilton, L. J.: Reprint No. 99, from Ven. Dis. Inform., 19, 396, 1938. (49.) Warthin, A. S.: South. Med. J., 24, 273, 1931. (50.) Zieler, K.: Deutsch. med. Wchnschr., 52, 49, 1926.

OTO-RHINO-LARYNGOLOGY

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THE LOCAL USE OF SULFONAMIDES IN NASAL AND SINUS INFECTION: AN ANALYTICAL REVIEW

By NOAH D. FABRICANT, M.D.

EARLIER in the year Long[21] declared that the introduction of sulfonamide compounds as prophylactic and curative agents in the field of surgery has not been an unmitigated blessing for surgeons because of a growing tendency to neglect fundamental principles of good surgical judgment and technique and to rely instead on the wholesale use of the "wonder drugs." In a limited sense, this judgment is equally applicable to the promiscuous local use of sulfonamides in nasal and sinus infection; for here, many physicians neglect the sound physiologic principles upon which rational nasal and sinus medication rests.

Rhinologists, in recent years, have placed special stress on nasal physiology and nasal histopathology—subjects, incidentally, to which most nose and throat textbooks attach insufficient importance—because to a great extent these two fields provide the quintessence of intelligent intranasal medication. Since the magic word "sulfonamide" has stirred the collective hopes of a sinus-conscious public and a sinus-sensitive medical profession, the purpose of this review is to attempt an evaluation of the published results concerning the local use of sulfonamides in nasal and sinus infection so as to bridge the gap between what meager laboratory investigation there has been and eventual clinical judgment.

The wide acceptance of a rationalized form of nasal and sinus therapy by the medical profession can be established only in the event of a clear understanding of the manner in which drugs work. Such an understanding is assisted materially by studying the effect of drugs on several very important factors: the behavior of the mucous membrane lining of the nose, ciliary action, nasal pH, and the production of systemic side-effects. Nasal medication harmful to ciliary action impairs a highly important function. Markedly alkaline drugs are very irritating to the nasal mucous membrane; drugs prompting pathologic change in the underlying mucous membrane are agents to be avoided. Drugs which induce toxic reactions following intranasal medication are undesirable and merit small consideration in routine practice. Conversely, non-toxic medication, compatible with ciliary action, possessing a physiologic nasal pH and non-traumatizing to the mucous membrane, is most useful in the treatment of nasal and sinus disease—for it functions on a rational, physiologic basis.

Effect on Nasal Mucous Membrane and Nasal pH. According to Futch[12] and his associates, the complexity of chronic sinusitis is known too well to expect an eradication of infection, degenerative pathologic changes, and the constitutional factors involved by the use of a single medicament. Chronic sinusitis is not a specific disease, and success cannot be expected when it is so treated. Their report on the effect of solutions of sodium

sulfathiazole in 5% and 30% concentrations when applied to the nasal mucous membranes of rabbits is of interest. It was found that a 5% solution of sulfathiazole sesquihydrate exerts an early and destructive effect on the nasal mucous membrane. The cilia and the superficial layers of columnar cells are, to a large extent, destroyed. Even after 1 week's rest from instillations, recovery does not take place. Hydrogen-ion concentration determinations revealed that both the 5% and the 30% solutions had a pH of approximately 10.

The effect of sulfathiazole solutions instilled in the noses of inbred Swiss mice was recently described by Hunnicutt.[16] The mice were treated with 0.5%, 1% and 5% solutions of sodium sulfathiazole. Since the 5% solution had been recommended in the medical literature, more extensive experiments were carried on with it. Instillations were made 3 times a day for 14 days. In order to determine if there were any intermediary changes, 3 mice were killed every twenty-four hours, including the 10th day, and then a final group was killed on the 14th day. Purulent exudate was found during the first 3 days in about half of the mice; after that the only finding was a slight excess of mucus. The most pronounced change occurred in the olfactory epithelium which was disorganized even though it was not destroyed. The sinuses showed purulent exudate, and the epithelium, particularly that lining the frontal sinuses, was highly inflamed. In this early group, in which a purulent exudate and inflamed mucous membrane was present, a number of the mice developed bronchopneumonia. When applied to the nasal mucous membrane, 0.5% and 1% solutions of sodium sulfathiazole produced the same types of reactions although the inflammation was less.

Gundrum[14] utilized 21 rabbits—the rabbit was thought to present a mucous membrane more nearly compatible to that of human beings than the mucous membrane of any other laboratory animal—to observe and study the effect of 4.7% solutions of sodium sulfathiazole, sodium sulfadiazine and butanoylsulfanilamide on the nasal mucous membrane. There seemed to be considerable discomfort and restlessness after prolonged application of the sulfanilamide derivatives. At autopsy, in all of the animals treated with sulfanilamide derivatives there was evidence of inflammation throughout the nose. This was more marked in those animals in which sodium sulfathiazole and butanoylsulfanilamide were used. Microscopic study of the sections from the animals in the series treated with sodium sulfathiazole and the series treated with butanoylsulfanilamide showed injury to the entire nasal mucous membrane and the destruction appeared greatest in the olfactory area. Sodium sulfadiazine, while not so completely destructive, was found to be definitely injurious.

A hydrogen-ion concentration near that normal to the mucous membrane is, according to Fantus,[8] a matter of even greater importance for applications to the mucous membranes than the matter of isotonicity. In this connection, Fabricant[7a, b, c] has reported the normal, physiologic nasal pH values of the human being to be in the range between approximately pH 5.5 and 6.5. He has suggested that during an attack of acute rhinitis, acute rhinosinusitis and the more active stages of allergic rhinitis, the employment of an appropriate nasal medicament which lowers the abnormal, alkaline pH found in these conditions to a normal, slightly acid level between 5.5 and 6.5—in short, a physiologic pH—is most desirable. Since the sodium salts of the sulfanilamide group are extremely alkaline, having a pH which ranges from 10 to 11, they are by no means free of undesirable caustic reactions because of the irritating properties associated

with its alkalinity. In addition to these unfavorable features, a further objection to their use has been the fact that solutions of sulfathiazole may become yellow on standing and decompose within a few days, especially when unprotected from daylight.

At the time Turnbull[32] overenthusiastically advocated the use by nasal spray of a 5% solution of sodium sulfathiazole in the treatment of chronic sinusitis, many physicians began a mass clinical trial before adequate laboratory investigation of the type just described had been undertaken. A warning, however, came from Fletcher,[10] who reported necrosis of the lining of the maxillary sinus following irrigations of the sinus with 5% and 10% solutions of sodium sulfathiazole over a 3 week period. He maintained that inasmuch as the sodium salts of sulfanilamide derivatives are extremely alkaline, they are very caustic, and in this case the solutions charred or burned the granulations and mucous membrane with which they came in contact.

The use of a 5% solution of sodium sulfathiazole by means of nasal tamponage Merica[24] found to be quite disappointing in cases of acute rhinitis but effective in certain types of sinusitis. Following the application of 5% cocaine solution, Merica employed nasal tampons moistened with sulfathiazole solution. In this connection, it is of interest to note that the preliminary use of cocaine solution produced anesthesia of the nasal mucous membrane as well as an acid nasal pH environment.[76] These two factors alone would be sufficient to counteract the usual intranasal distress produced by sodium sulfathiazole solutions. Despite the combined use of cocaine solution and sodium sulfathiazole solution, Merica observed some patients who did not tolerate the application; these patients developed reactions resembling an allergic rhinitis. A similar phenomenon has been noted by Bordley[2] and his associates. According to Fenton,[9] none of the combinations of sulfathiazole with vasoconstrictors is free from the possibility that allergic responses may be excited in susceptible persons, and it does not seem possible to determine in advance whether such sensitivity exists.

To obviate the strong alkalinity, irritating properties and deterioration of such solutions as have been discussed, Yonkman[35] and his associates have dissolved various sulfonamides in propylene glycol. The most useful of these propylene glycol preparations they believe to be a combination with a 3% solution of sulfathiazole, 3% solution of sulfapyridine and a 10% solution of sulfanilamide. The pH of these solutions is slightly acid and approximates normal, physiologic nasal pH values. Blackford[1] found a 3% solution of sulfathiazole in propylene glycol when used locally to be non-irritating and non-toxic. The preparation can be used generally in large amounts without untoward results. However, he believes further experimentation should be done in regard to the effect of this preparation on the ciliary action in the nose before any definite conclusions as to the advisability of using it extensively in acute upper respiratory infections can be drawn. Stovin[30] finds that a combination of sulfanilamide and allantoin lends itself to use in intranasal therapy; it is slightly acid with a pH of 5.4. Colloidal silver preparations of sulfanilamide, sulfathiazole, sulfapyridine and sulfadiazine have been investigated by Wruble.[34] With the exception of the silver sulfanilamide, which darkens rapidly, the others remain as white or cream-white powders, easily dispersible in water. Solutions of colloidal silver sulfathiazole have a slightly acid pH which is in the range of maximum effectiveness. It is possible that such non-irritant chemical combinations of the sulfonamides, after further study, may in time prove useful.

Clinical Reports. A small but steady stream of clinical reports[3, 19, 22, 28] has appeared in the medical literature. In attempting to establish the usefulness of local applications of sulfonamides to infections of the nose and sinuses, the preponderant majority of writers appear to neglect the entire body of knowledge known as nasal physiology. That the local administration of chemotherapeutic agents is substantially without influence upon the common cold is almost generally agreed. Since the literature on their value in sinusitis is still limited, the cross-currents of opinion preclude final judgment. At this juncture, it is well to remember that over a span of many years numerous agents have been introduced into the sinuses—particularly the maxillary sinus—immediately after lavage. The very multiplicity of these agents indicates the inadequacy of many of them; this is in itself evidence that the ideal treatment has not been found.

It was Turnbull[32] who first described the intranasal use of a 5% solution of sodium sulfathiazole in chronic sinusitis. After instilling it directly into the sphenoid and maxillary sinuses, he was unable to draw any conclusions regarding clinical improvement; but after spraying the nose, he saw definite improvement clinically. It is possible that what was observed as increased drainage from the nose following sulfathiazole spraying was in all likelihood due to the irritating qualities of the markedly alkaline medication rather than a free flow of discharge from the sinuses.

Bordley[2] and his associates believe that many nose and sinus complications may be prevented by spraying the nasal passages and pharynx with a 2.5% sulfadiazine triethanolamine solution. The concentration of sulfadiazine in the mucous membranes of the upper passages was not determined. Brown[4] finds that sulfonamide powder may be applied to the mucous membrane of the sinuses by the intranasal route and that the powder seems to be more effective than the solution in cases of chronic purulent sinusitis, probably because of its more lasting contact with the mucous membrane. Connell and Trowbridge[6] maintain that acute nasal infections respond best to the local use of sulfanilamide powder and chronic rhinitis best to sulfathiazole powder. It was found that coarse powder was not adaptable for use in the nasal cavities. Moderately fine or fine powder, of a 40 to 100 mesh character, proved to be the most satisfactory. Marks[23] states that a 20% or 50% sulfathiazole jelly is an effective therapeutic agent when injected into the maxillary sinus in which there is evidence of chronic maxillary sinusitis. A suspension of sulfathiazole appeared more effective than sodium sulfathiazole in clinical practice. Van Alyea,[33] however, questions the value of sulfonamide preparations instilled locally into the maxillary sinus. Kern[18] is of the opinion that sulfanilamide and gauze packing can be used satisfactorily after submucous resection, ethmoidectomy, and intranasal antrotomy. When the packing is removed in 24 hours, there seems to be less swelling of the mucous membrane and more rapid healing. Freeman[11] describes a method of treating acute infections of the nasopharynx and pharynx. He writes that the possibility of systemic damage from the use of sulfathiazole is negligible and can be carried out on ambulatory patients.

Lindsay[20] asserts that in chronic suppuration of the maxillary, frontal and ethmoid sinuses, he was unable to satisfy himself that sulfathiazole used locally after irrigation was of any definite benefit. He employed suspensions of finely ground sulfathiazole, in concentrations up to 30%, which could be introduced through a cannula. In treatment of acute infections of the sinuses, Lindsay declares, the suppuration is seldom limited to one sinus; there is usually more or less general infection of the upper respiratory

tract, with involvement of several sinuses. Therefore the treatment, for example, of the maxillary sinus alone cannot be expected to relieve the accompanying inflammatory process in the anterior ethmoid cells, or in the upper respiratory tract in general. The use of a 2.5% solution of sulfadiazine (with triethanolamine) as a spray did not shorten the course of sinus infection. The material was employed in a few cases by the displacement method and produced fairly severe discomfort, lasting nearly 24 hours. The pH of the solution is about 8.5, and attempts to lower the percentage of triethanolamine so as to reduce the pH have caused precipitation. It is believed that the local use of sulfonamide compounds does have a place in postoperative treatment of sinuses where a radical operation has been performed with removal of diseased mucous membrane. The effects here are similar to those in surgical wounds elsewhere, and the action in keeping down infection is unmistakable. In Furstenberg's[12] experience, sulfanilamide when used locally in septic wounds tends to shorten the period of convalescence, prevent troublesome local reactions and allay discomfort. It is unnecessary and undesirable to use it in a clean wound. Confidence in local chemotherapy is justified only when it is employed as an adjunct to an operation which is performed with credit to the surgeon and safety to the patient.

A recent publication of Silcox and Schenck[29] concerns itself with the use of microcrystalline forms of drugs of the sulfanilamide group. Their clinical study included patients treated with the microcrystals of a drug of the sulfanilamide group in 5% suspension in a physiologic solution of sodium chloride and a group of patients treated with microcrystals of sulfathiazole in a 5% suspension in 1% aqueous solution of paredrine hydrobromide (p-hydroxy-a-methylphenethylamine hydrobromide) which has a vasoconstrictor action. Levels of sulfathiazole in the blood taken in some of the early cases convinced the investigators of the comparative safety with which drugs of the sulfanilamide group can be used locally. No studies were made to determine the effect of the drug histologically on the nasal mucous membrane. In the group treated with a suspension of sulfathiazole in a solution of paredrine hydrobromide there was a rise in systolic blood pressure of 10 to 15 points after displacement irrigation. Microcrystalline preparations were found to be effective in the treatment of acute infections of the upper respiratory tract, of acute sinusitis, and in selected cases of chronic sinusitis. Sulman[31] used a suspension of sulfathiazole in an aqueous solution of paredrine hydrobromide and found it to be successful in reducing nasal congestion and in decreasing or eliminating discharge. No untoward effects of any kind were observed. Its use was believed to have shortened the course of infection for many patients and averted sequelæ to colds. Toxic reactions produced by this preparation are described as occurring in 2 cases by O'Donnell.[25]

Harris[15] and his associates discuss their experiences with the administration of sulfonamides by inhalation, by introducing sulfonamide "smoke" into the air. The "smoke" utilized in these experiments was derived from a 5% aqueous suspension of sulfathiazole microcrystals. The suspension was introduced into an atomizer supplied with compressed air which produced a finely divided spray. The resultant spray was led into a chamber containing Swiss white mice. Gross examination of the lungs at different intervals up to several days after the inhalation revealed mild hyperemia soon after the inhalation. Mice exposed to a spray of sodium sulfathiazole solution under similar conditions died within a few hours

and their lungs showed gross evidences of an extreme hyperemia. According to the authors, the pharmacologic experiments demonstrate that sulfathiazole can be administered by inhalation and produce satisfactory blood levels. Elsewhere,[5] it is stated by one of the investigators that three deep breaths in the adult taken while the "smoke" is being blown through the nose and/or mouth produce a sulfonamide blood level of 3 to 5 mg. per 100 cc. of blood in less than 15 minutes, as measured at the finger-tip. This level rises for some hours to approximately double the original figures and at the end of 2 days is usually still above 1 mg. per 100 cc.

Ivy and Goetzl[17] review the literature on the pharmacology of the drug known as d-desoxyephedrine hydrochloride. Recently the vasoconstrictor dl-desoxyephedrine hydrochloride, 0.125%, has been combined with 2.5% solution sodium sulfathiazole and is available for use in the nose and paranasal sinuses. A review of the literature indicates that d-desoxyephedrine hydrochloride has an action on man and on animals similar to that of amphetamine sulfate. It is more potent per milligram than amphetamine sulfate. Although a number of German authors have stated that d-desoxyephedrine hydrochloride is not habit-forming, it was placed under the German narcotic law with the warning that the physician employing it should exercise caution.

Among the case records of the Massachusetts General Hospital[27] is one dealing with an allergic middle-aged woman who had applied over a period of weeks sulfathiazole ointment to a fissure at the tip of the nasal ala. Prior to hospitalization she had also taken sulfathiazole by mouth. When a generalized skin eruption developed, she was admitted to a community hospital. She failed to respond to appropriate therapy and died of a "sulfathiazole nephritis." At the subsequent clinicopathologic conference the question of the treatment of the fissure about the tip of the ala with sulfathiazole ointment in a patient known to be allergic was raised. "Unless one believed that was a potentially dangerous lesion, which it could be if badly infected, one should not run the risk of sensitizing a person to a drug that may be a life-saving one later."

Comment. The haste with which some members of the medical profession and the general public have responded to the cry that the local use of sulfonamides in nasal and sinus infection is an effective "cure-all" is not without some apparent danger. Knowledge of the normal physiology of the lining mucous membrane of the nose and sinuses received its chief impetus in this country from the studies of a number of American investigators. Despite their efforts to familiarize physicians with the importance of nasal physiology and its immediate relationship to rational, physiologic nasal medication, certain fundamental principles appear to have been overlooked in the local application of various sulfonamide preparations indiscriminately employed in nasal and sinus infection.

Such factors as the effect of a nasal medicament on the mucous membranes of the nose and sinuses, its relationship to ciliary action and nasal pH, and the degree of toxicity which is sometimes produced by absorption from the mucous membrane are always of propitious consideration in establishing the value of a nasal preparation. The fact that alkaline preparations of sodium sulfathiazole solutions injure the mucous membrane is sufficient to indict it on that score. Furthermore, the destruction of cilia—and consequently the impairment of ciliary function—together with its deviation from a physiologic nasal pH, as well as the disorganization of the olfactory epithelium which such preparations establish, plus

the production of bronchopneumonia in laboratory animals, cannot justify the indiscriminate selection of sodium sulfathiazole preparations for use in the human nose.

The recent introduction of a number of sulfathiazole preparations in alkaline combination with a nasal vasoconstrictor raises several pertinent questions. Nasal vasoconstrictors, Proetz[26] declares, are probably the most important single group of drugs available to the rhinologist. In terms of clinical evaluation, it is therefore extremely difficult to interpret the benefits to be gained by a patient receiving a form of combined intranasal medication. The vasoconstrictor action of some nasal vasoconstrictors is powerful and may conceivably lead to a partial, and in some cases, total (although transitory) anoxia. Some of the cells may suffer damage, but this is reparable with the decrease of the vasoconstrictor effect. It is possible that the damage might be more if the sulfonamide preparations are present. In any event, there is need for further evidence of its innocuousness other than a simple clinical observation.

The degree of toxicity that may be produced by sulfonamides is equally deserving of scrutiny. Patients employing sulfonamides locally are potentially subject to all the risks entailed by oral or parenteral administration. In a therapeutic field as new as this, physicians should be on their guard as to the possibility of such complications as allergic rhinitis, toxic dermatitis, jaundice, hematuria, blood dyscrasias, hyperpyrexia, central nervous system effects, weakness and pallor, and nausea and vomiting. Finally, unintelligent and promiscuous usage locally of sulfonamide preparations may develop in the patient a sulfa-resistant state. In general, such resistance is by no means a theoretical matter.

With respect to the rôle of the local use of sulfonamides in nasal and sinus infection, the clinician should not on the basis of inconclusive clinical evidence run too far ahead of competent and painstaking laboratory evidence. While the evidence to date would seem to indicate caution in the use of some of the sulfonamide preparations in the nose and sinuses, others are employed successfully in a limited number of directions. These do have an important place in contemporary rhinology. Indeed, it is quite possible that the near future may see the further introduction of sulfonamide preparations which locally are non-toxic and which are compatible with the tenor of modern-day nasal physiology. Such agents, however, may in time prove useful only as an important adjunct to the effective treatment of nasal and sinus infection, rather than as a universal "cure-all."

REFERENCES

(1.) Blackford, R. W.: Laryngoscope, 53, 164, 1943. (2.) Bordley, J. E., Crowe, S. J., Dolowitz, D. A., and Pickrell, L.: Ann. Otol., Rhinol. and Laryngol., 51, 936, 1942. (3.) Bowers, A. C.: Bull. New York Acad. Med., 17, 453, 1941. (4.) Brown, L. A.: Ann. Otol., Rhinol. and Laryngol., 51, 611, 1942. (5.) Chapple, C. C.: J. Am. Med. Assn., 122, 695, 1943. (6.) Connell, E. S., and Trowbridge, B. C.: Arch. Otolaryngol., 35, 740, 1942. (7.) Fabricant, N. D.: (a) Arch. Otolaryngol., 33, 150, 1941, (b) Ibid., 34, 297, 1941; (c) Ibid., 34, 302, 1941. (8.) Fantus, B.: Technic of Medication. Am. Med. Assn. Press, 1938. (9.) Fenton, R. A.: Arch. Otolaryngol., 37, 491, 1943. (10.) Fletcher, R.: California and West. Med., 55, 94, 1941. (11.) Freeman, M. S.: Arch. Otolaryngol., 37, 496, 1943. (12.) Furstenberg, A. C.: Laryngoscope, 53, 93, 1943. (13.) Futch, C. E., Rosenvold, L. K., and Stewart, C. E.: J. Am. Med. Assn., 119, 7, 1942. (14.) Gundrum, L. K.: Arch. Otolaryngol., 37, 209, 1943. (15.) Harris, T. N., Sommer, H. E., and Chapple, C. C.: Am. J. Med. Sci., 205, 1, 1943. (16.) Hunnicutt, L. G.: Arch. Otolaryngol., 36, 837, 1942. (17.) Ivy, A. C., and Goetzl, F. R.: War Med., 3, 60, 1943. (18.) Kern, E. C.: Arch. Otolaryngol., 36, 134, 1942. (19.) Klestadt, W. D.: J. Am. Med. Assn., 118, 998, 1942. (20.) Lindsay, J. R.: Arch. Otolaryngol.,

37, 604, 1943. (21.) **Long, P. H** : J. Am. Med. Assn., 121, 303, 1943. (22.) **Mac-Arthur, R. S.**: Clin. Med., 49, 101, 1942. (23.) **Marks, R. F.**: Arch. Otolaryngol., 35, 794, 1942. (24.) **Merica, F. W.**: J. Am. Med. Assn., 119, 286, 1942. (25.) **O'Donnell, M. C.**: J. Am. Med. Assn., 122, 298, 1943. (26.) **Proetz, A. W.**: Arch. Otolaryngol., 37, 15, 1943. (27.) **Richardson, W.**: New England J. Med., 228, 668, 1943. (28.) **Scal, J.**: Eye, Ear, Nose and Throat Monthly, 21, 310, 1942. (29.) **Silcox, L. E.**, and **Schenck, H P.**: Arch. Otolaryngol., 36, 171, 1942. (30.) **Stovin, J. S.**: Eye, Ear, Nose and Throat Monthly, 22, 175, 1943. (31.) **Sulman, L. D.**: Arch. Otolaryngol., 37, 713, 1943. (32.) **Turnbull, F. M.**: J. Am. Med. Assn., 116, 1899, 1941. (33.) **Van Alyea, O. E.**: Trans. Am. Acad. Ophth. and Otolaryngol., 46, 69, 1941. (34.) **Wruble, M.**: J. Am. Pharm. Assn., 32, 80, 1943. (35.) **Yonkman, F. F.**, **Craver, B. N.**, and **Chase, H. F.**: J. Am. Med. Assn., 118, 317, 1942.

BOOK REVIEWS AND NOTICES

THE MEDICAL CLINICS OF NORTH AMERICA. Symposium on Infectious and Tropical Diseases. (Vol. 27, No. 3, May 1943.) Pp. 881; many illus. Philadelphia: W. B. Saunders Company, 1943. Price, year, $16.00.

THIS number is especially welcome at this time, offering as it does concise and authoritative reviews on a number of the most important tropical diseases, as well as on certain other borderline diseases. The discussions aim at being practical rather than exhaustive, yet space has been found to present the newest and most up-to-date conceptions of transmission, diagnosis and treatment. Preventive aspects are also stressed, as would be expected from a group of contributors, many of whom are workers in the field of Public Health or Preventive Medicine.

The subjects on the whole are well chosen, prominence being given to malaria and dysentery, typhus and relapsing fever, all diseases which may easily assume epidemic proportions with our armed forces. The Reviewer would have been pleased to see a fuller discussion of the dysenteries, but doubtless space forbade. Trypanosomiasis, filariasis, schistosomiasis, dengue, plague and cholera are discussed by masters in the field, the presentations coming to us out of years of personal experience in many instances. The names of Dyer, Strong, Simmons and Russell, to mention but a few, are evidence of the authoritative character of the contributions. It would be impossible to cover the whole field of tropical diseases in one slender volume, and further volumes to supplement these studies would be very desirable.

It seems not inappropriate at this time when tropical diseases are being brought to America in increasing numbers, to find them discussed side by side with other infectious diseases which cause much concern in the United States. Among these latter are the epidemic encephalitides, coccidiodomycosis and primary atypical pneumonia. Well-known workers in these fields crystallize for us the recent knowledge and views on each subject. Late reports and conclusions regarding diseases longer known to the medical profession form the basis for other valuable articles and round out a series of unusual significance. No doctor would wish to miss an acquaintance with this symposium on infectious and tropical diseases.   J. M.

THE NEUROMUSCULAR MATURATION OF THE HUMAN INFANT. By MYRTLE B. McGRAW, Associate Director, the Normal Child Development Study, Department of Pediatrics, Columbia-Presbyterian Medical Center. Pp. 154; some illustrations. Morningside Heights, N. Y.: Columbia University Press, 1943. Price, $2.00.

THE studies reported in this volume cover more than a decade of observation on the development of function in the newborn and infant child. The investigation originated in an attempt to correlate the development of activity with the anatomic maturation of the cells of the human cortex, a problem upon which Dr. Frederick Tilney was working before his death.

The general plan was to examine some particular function, for example, the behavior of the child in water, and trace the development of this behavior until a point was reached in which deliberate or voluntary control appeared to be exercised on that function. At this time, it was assumed by Dr. McGraw, the cerebral cortex began exerting its effect. For example, the newborn child, when placed in water, will swim, reflexly it is presumed. At a later date this type of activity gives way to disorganized, struggling movements; and still later, to voluntary swimming.

The various actions studied cover the range of early motor behavior in the

infant. Among these are: grasping, postural reflexes, rolling over, crawling, creeping, sitting, rising, and walking.

Due to Dr. Tilney's untimely death, the anatomic evidence on the maturation of the human cortex is still lacking, so that the author's original aim has not been achieved. Nevertheless some conclusions have emerged from this study which will appeal to a wider audience than her original thesis would interest.

Dr. McGraw suggests that her studies point the way to a better method of training children. Among her conclusions are: it is futile to attempt training before the neural mechanisms have developed sufficiently; exercise of a newly developing function may advance the achievement beyond the stage normally expected; transition from one type of activity to another is characterized by disorganization and confusion; the behavior pattern will tell when a child is ready to undertake a new type of activity; it is just as important to know when to diminish training as when to begin it. Obviously the conclusions from a study of these motor actions are in some way applicable to more complicated intellectual development.

This work can be commended highly for its succinct summary of these important studies. G. G.

LABORATORY EXPERIMENTS IN PHYSIOLOGY. By W. D. ZOETHOUT, PH.D., Professor of Physiology in the Chicago College of Dental Surgery (Loyola University). Third ed. Pp. 256; 88 illus. St. Louis: The C. V. Mosby Company, 1943. Price, $2.25.

A DESCRIPTION of apparatus commonly used in the elementary physiology laboratory is followed by procedures for an ample number of simple experiments illustrating fundamental physiological principles, stressing the nerve muscle, cardiovascular, respiratory systems, and special senses. Judicious selection of experiments from this manual should result in an adequate laboratory accompaniment to a course in elementary physiology for college or dental school. For the most part, apparatus illustrated and described is made by the Harvard Apparatus Company, but the experiments are adaptable to other types.

Part II of the manual consists of a few simple experiments of a chemical nature illustrating tests for carbohydrates, fats, and proteins, the fundamentals of digestion, and of urinalysis. A. C.

BLOOD GROUPS AND TRANSFUSION. By ALEXANDER S. WIENER, A.B., M.D., Serologist and Bacteriologist in the Office of the Chief Medical Examiner of New York City, Head of Transfusion Division, Jewish Hospital of Brooklyn, New York. Third ed. Pp. 438; 69 figs., 106 tables. Springfield, Ill., and Baltimore, Md.: Charles C Thomas, 1943. Price, $7.50.

IN every hospital's experience transfusion reactions of the hemolytic type occur more frequently than textbook statistics would indicate, even when the technique of administration lies above reproach. Fortunately the symptoms are usually but slight or moderate, though violent and even fatal "accidents" are noted at times. Any such reaction is not only potentially dangerous; its presence signifies that the administered blood has been destroyed, wholly or in part, and to that extent the therapeutic intention of the transfusion has not been achieved. The only way to assure complete safety and efficiency with every transfusion is to give the physicians in charge a full understanding of the complementary sciences of transfusion and of grouping.

For this reason one welcomes the publication of the third and thoroughly up-to-date edition of this well-known authoritative monograph, with its excellently organized body of information and interpretation. The first third of the book discusses in detail the properties of the known blood agglutinogens, not only A and B but also A₁, A₂, M, N, P, Rh and Hr, singly and in combination. Included are chapters on sources of error in blood grouping, history

and techniques of blood transfusion, reactions and complications following transfusion, and the preparation and storage of blood, plasma and serum. Next comes a learned but extremely readable presentation of the individual differences in human (and animal) bloods in relation to heredity and anthropology. Statistics have been kept to a minimum, with the symbols and methods used explained lucidly in advance. The final portion of the book deals with recent progress, such as the important relationship of the Rh factor to erythroblastosis fetalis and to hemolytic reactions during pregnancy or after multiple transfusions. Medico-legal applications of blood tests in disputed parentage, and the individual identification of stains in forensic cases, are gone into extensively. All chapters reflect the wealth of experience of the author.

I. W.

THE PRACTICE OF REFRACTION. By SIR STEWART DUKE-ELDER, M.A., D.Sc. (ST. AND.), PH.D. (LOND.), M.D., CH.B., F.R.C.S., Surgeon-Oculist to H. M. The King; Ophthalmic Surgeon and Lecturer in Ophthalmology, St. George's Hospital. Fourth ed. Pp. 328; 183 illus. Philadelphia: The Blakiston Company, 1943. Price, $4.50.

THE aim of this book, as of the 3d edition from which it differs in only minor respects, is to present the essential principles of the theory and practice of the correction of defects in the optical system of the eyes and their associated muscles. Clinical methods and criteria are stressed. Not undue emphasis is laid upon the consideration of the general bodily welfare as well as the local ocular state. The subject of aniseikonia is introduced. Many in this country would disagree with the author concerning the use of orthoptics and/or surgery in cases of squint. And, also, many would use cycloplegics more freely than he recommends. On the whole, however, the book is a valuable addition to the library of one familiar with the subject, as well as that of the beginner.

P. M.

TABLES OF FOOD VALUES. By ALICE V. BRADLEY, M.S., Associate Professor of Nutrition and Health Education, State College, Santa Barbara, Calif. Pp. 224. Second ed. Peoria, Ill.: The Manual Arts Press, 1942. Price, $3.50.

THIS is an excellent book for the purpose for which it is intended, namely "to calculate an individual's diet quickly in an approximate way."

The book is easily read; the figures are large enough to be quickly read and the naming of foods on each side of the tables is a big aid for speed. The tables are comprehensive and the many recipes included certainly add to the value of the book for the lay person. The fact that the tables give both the weight in grams and the approximate measure adds to the value of the book for everyone using it.

E. M.

CLINICAL ROENTGENOLOGY OF THE CARDIOVASCULAR SYSTEM. By HUGO ROESLER, M.D., F.A.C.P., Temple University School of Medicine, Temple University Hospital, Philadelphia. Second ed. Pp. 480; 337 figs. Springfield, Ill.: Charles C Thomas, 1943. Price, $7.50.

THIS 2d edition brings up to date the most comprehensive presentation of the subject in the English language. The technique and apparatus used in the various methods of roentgenologic study; the anatomy, physiology and roentgenologic aspects of the normal and abnormal cardiovascular apparatus and its subdivisions; cardiovascular disease from the viewpoint of etiology and structural changes and methods of measurement are all adequately discussed and well illustrated. Their integration with clinical data makes the book particularly valuable. A full bibliography with each chapter and a good index are appended. The following suggestions are offered for improvement of a future edition: the use of the terms "dorsad" and "ventrad" is somewhat

confusing and stilted in view of man's erect posture and the widely accepted use of the terms "anterior" and "posterior"; the use of numerous black and white arrows instead of numbers in many of the illustrations requires a tedious search in the lengthy captions for identification; despite the author's fear of breaking continuity, specific facts in the text should be numerically related to the chapter bibliographies to enhance the value of the book as a ready reference text. However, the book is unreservedly recommended as required reading for students of roentgenology and cardiovascular disease. A. M.

FLYING MEN AND MEDICINE. The Effects of Flying Upon the Human Body. By E. OSMUN BARR, M.D. Pp. 254; 8 figs, 1 colored plate. New York and London: Funk & Wagnalls Company, 1943. Price, $2.50.

AN interesting and adroitly written book about aviation medicine in unusually simple language for the non-technical reader. Anyone who wishes to catch up on this most recent aspect of medicine without being overburdened by a mass of physiologic and technical details should read this entertaining volume. It is sufficiently complete and contains many interesting and instructive diagrams. The book is especially recommended to the young aspirant for wings. W. S.

RENAL LITHIASIS. By CHARLES C. HIGGINS, M.D., Cleveland Clinic, Cleveland, O. Pp. 122; 18 illus. Springfield, Ill.: Charles C Thomas, 1943. Price, $3.00.

THIS brief treatise, the annual Beaumont Lecture for 1942, is by a recognized authority on renal lithiasis. The author, an assiduous research worker, has given us something which is a pleasure to read. Dr. Higgins writes with the authority of years of clinical experience, and backed by the entire research personnel of the Cleveland Clinic.

Starting with a delightful though brief history of renal lithiasis, he follows with a lucid exposition of the etiology, always leaning toward his own belief in the part played by diet and vitamin A deficiency. There follow 7 pages on symptomatology, 15 devoted to the surgical handling of the problem, and 15 more on the dietary treatment. The book ends with 16 pages devoted to recommended diets for restricting the intake of unwanted salts, for increasing the vitamin A, and for acidifying or alkalinizing the urine. A. R.

UROLOGY IN GENERAL PRACTICE. By NELSE F. OCKERBLAD, B.S., M.D., F.A.C.S., Professor of Clinical Urology, University of Kansas School of Medicine; Senior Attending Urologist to St. Luke's Hospital; Consulting Urologist to the Children's Mercy Hospital, Kansas City, Mo.; and HJALMAR E. CARLSON, B.S., A.M., M.D., F.A.C.S., Instructor in Urology, University of Kansas School of Medicine; Attending Urologist to St. Luke's Hospital and Trinity Hospital, Kansas City, Mo. Pp. 383; 98 figs. Chicago: Year Book Pub., 1943. Price, $4.00.

THIS small, practical manual should be useful as an easily read outline of the subject to student, practitioner, and specialist.

There is a chapter on urologic diagnosis which gives one a well-balanced idea of the approach to the urologic patient. The information presented should help a physician to decide which cases can be best taken care of by the general practitioner and which cases require the care of experts in the field.

The use and care of catheters, sounds, and other diagnostic and therapeutic urologic equipment are discussed. Contraindications to the use of such materials are presented.

The discussion of the various diseases of the urinary organs is thorough and important practical points in the diagnosis and treatment are given. There is

a separate chapter on the so-called "medical diseases" of the kidney. The authors think that nephritis and allied conditions are best handled under the supervision of the urologist.

The discussion of urinary lithiasis contains the usual information presented on the subject and in addition mentions the most recent contribution to the knowledge of the etiology of urinary stone, that is Randall's papillary lesion.

There is an entire chapter devoted to carcinoma of the prostate. This one-time therapeutic enigma can be so handled that these patients can live on with a fairly normal existence. Treatment with stilbestrol and bilateral orchidectomy is discussed.

The chapters on the use of sulfonamides in urologic infections, both gonorrheal and non-specific, are a bit sketchy considering the great advance that the introduction of these substances afforded. The proprietary drug "sulamyd" is recommended by the authors on several occasions for the treatment of non-specific types of urinary infections; but evidence in the literature and from those who have had personal experience in the use of this drug would not indicate that its therapeutic effects warrant such high esteem as here presented.

The inclusion of a bibliography would increase the value of the book to anyone desiring further information on any subject presented. L. LA T.

AN INTRODUCTION TO GROUP THERAPY. By S. R. SLAVSON, Director of Group Therapy, Jewish Board of Guardians, New York, formerly Lecturer, School of Education, New York University. Pp. 352. New York: The Commonwealth Fund, 1943. Price, $2.00.

THIS book is the outgrowth of 8 years' experience of the Jewish Board of Guardians of New York City. Group therapy is "not merely group activity but a method of psychotherapy to be employed along with psychiatric case work and psychologic services and only after a diagnostic examination indicates that it is needed." It may be used as exclusive treatment or as supplementary to individual treatment.

The principles and practices of group therapy are described and descriptions of actual cases and case treatments are given. This book should be of great value not only to the clinical worker but to teachers and administrators in our schools. It reveals unsuspected values in group work that may be very suggestive in the pupil activity program even though many of the specific methods described would be quite unsafe in the hands of a teacher untrained in psychiatric case work. A. J.

A MANUAL OF PULMONARY TUBERCULOSIS (PART I) AND AN ATLAS OF THORACIC ROENTGENOLOGY (PART II). By DAVID O. N. LINDBERG, M.D., F.A.C.P., Lecturer on Tuberculosis, State University of Iowa, College of Medicine. Pp. 219; 189 illus. Springfield, Ill.: Charles C Thomas, 1943. Price, $6.50.

IN this book Part I presents a discussion of the diagnosis and treatment of pulmonary tuberculosis and the author has wisely included a chapter dealing with modern methods of control. Numerous charts and graphs are used to good advantage and the illustrations are of excellent quality. Part II is purely an atlas of radiographic reproductions comprising 145 plates. The roentgenologic aspects of tuberculous pulmonary disease are amply portrayed, including results following treatment by conservative measures as well as by various surgical procedures. In addition, the characteristic radiologic findings of many of the more frequently encountered intrathoracic lesions other than tuberculosis are also presented. The plates are uniformly good.

Although the author emphasizes his desire for "brevity and sequence" and avoidance of "theoretical, experimental or controversial subjects," it would seem that the extreme brevity, so obvious in certain portions of the text, has detracted from the value of this work. However, the material is presented in a concise manner and clarity has been maintained throughout. H. I.

NEW BOOKS

An Atlas of Anatomy. By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S. (Edin.), Professor of Anatomy in the University of Toronto. Vol. 1, Upper Limb, Abdomen, Perineum, Pelvis, and Lower Limb. Pp. 214; 227 figs. Baltimore: The Williams & Wilkins Company, 1943. Price, $5.00.

The Conquest of Epidemic Disease. A Chapter in the History of Ideas. By Charles-Edward Amory Winslow. Pp. 411. Princeton, N. J.: Princeton University Press, 1943. Price, $4.50.

Hospital Discharge Study. Vol. 2, Hospitalized Illness in New York City. By Neva R. Deardorff, Ph.D., and Marta Fraenkel, M.D. Pp. 349; 105 tables. Welfare Council of New York City, 1943. Price, $1.00.

> This report is the second of the 3 volume publication *Hospital Discharge Study* (an analysis of 546,623 patients discharged from hospitals in New York City in 1933). It abstracts and studies 24 items of information on these patients covering their medical, demographic and social conditions and certain details on hospital stay. The volume contains a wealth of statistical information and demonstrates the value of and need for a more intensive study of hospital records.   R. B.

Papers From the Second American Congress on General Semantics. Non-Aristotelian Methodology (Applied) for Sanity in our Time. Compiled and Edited by M. Kendig. Pp. 579. Chicago: Institute of General Semantics, 1943. Price, $5.00.

Reconstructive Surgery of the Eyelids. By Wendell L. Hughes, M.D., F.A.C.S., Hempstead, N. Y. Pp. 160; 36 plates. St. Louis: C. V. Mosby Company, 1943. Price, $4.00.

Self-teaching Tests in Arithmetic for Nurses. By Ruth W. Jessee, R.N., M.A. Pp. 111. St. Louis: C. V. Mosby Company, 1943. Price, $1.50.

Kaiser Wakes the Doctors. By Paul de Kruif. Pp. 158. New York: Harcourt, Brace & Co., 1943. Price, $2.00.

Doctor Pryor: An Autobiography. By Dr. J. W. Pryor. Pp. 312; 17 illus. Cynthiana, Ky.: The Hobson Press, 1943. Price, $3.00.

Applied Anatomy of the Head and Neck. For Students and Practitioners of Dentistry. By Harry H. Shapiro, D.M.D., Assistant Professor of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 189; 173 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $5.50.

Essays in Biology. In Honor of Herbert M. Evans. Written by His Friends. Pp. 687; many illus. Berkeley and Los Angeles: University of California Press, 1943. Price, $10.00.

NEW EDITIONS

Chemical Spectroscopy. By Wallace R. Brode, Professor of Chemistry in the Ohio State University. Second ed. Pp. 677; 41 plates. New York: John Wiley & Sons, Inc., 1943. Price, $7.50.

An Introduction to Sociology and Social Problems. By Deborah M. Jensen, R.N., B.Sc., M.A., Instructor in Sociology and Social Problems at Schools of Nursing of St. Louis City Hospital and St. Luke's Hospital; Lecturer in Nursing Education, Washington University; Formerly Social Service Consultant to the Visiting Nurse Association, St. Louis. Second ed. Pp. 420; 78 figs. St. Louis: C. V. Mosby Company, 1943. Price, $3.25.

Family Nutrition. Published by the Philadelphia Child Health Society, 311 S. Juniper St., Philadelphia 7, Pa. Pp. 119; many tables and figures. Second ed. Price, 50 cents (special prices on quantity orders of 10 copies and more).

> In 1942 the 1st edition of the monograph was published by the Philadelphia Child Health Society. Since that time, additional needs have become important enough to publish a 2d edition of this booklet a year later. Much of the material is essentially the same as in the 1st edition—the important addition being a chapter on menu planning and rationing for wartime nutrition needs. The other chapters and tables have been brought up to date.   E. F.

NEW NOTICE TO CONTRIBUTORS AND SUBSCRIBERS

ORIGINAL ARTICLES

THE RECOGNITION OF MENINGOCOCCIC INFECTIONS

By Paul S. Strong, Captain, M.C.

FT. EUSTIS, VA.

(From the Station Hospital)

The present day concept of the morbid processes involved in the pathogenesis of meningococcic meningitis grew out of observations made during World War I. During an epidemic at an Army Post, Herrick[3] was able to recognize about 45% of his cases in the pre-meningeal stage, and about 4% of these failed ultimately to show signs of meningeal involvement. The finding of the meningococcus in the blood stream of these early cases led him to describe the pathologic process as that of a primary sepsis followed in most, but not all instances, by a secondary meningeal localization. The path of infection of the meningococcus and the resistance of different individuals may be shown diagramatically as in Figure 1.

Meningococcal infection of the nasopharynx is probably of short duration and in the majority of cases produces few or no symptoms.[1,4] Long[5] believed that the high incidence of upper respiratory tract infections in his series of meningitis cases was probably a seasonal occurrence, because the majority of the cases occurred in a period when respiratory tract infections were common. The involvement of the blood stream is the earliest stage where significant recognizable symptoms occur. Hemorrhages into the skin, mucous or serous membranes are characteristic of meningococcal sepsis, but sufficient emphasis has not been placed on the diagnostic value of these lesions. It is possible that this may be due to the apparent infrequency with which the rash is encountered in interepidemic meningitis. Craster and Simon[2] stressed the importance of skin hemorrhages in meningococcic infections, stating that they are as specific for that condition as is the rash of measles or scarlet fever.* Describing an epidemic of meningococcic meningitis, Smithburn et al.[6] noted petechiæ in 68% of 144 cases. Herrick considered petechiæ to be of diagnostic value and noted the sign in about one-half of his cases. Of 92 cases which form the basis

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* Hence the older use of the term "spotted fever," now wisely discarded as it was also used for typhus and Rocky Mountain spotted fever.—Editor.

of this report, 82% had petechiæ present either at the time of admission to the hospital or shortly thereafter.

It is our belief that the petechial rash occurs much more frequently in epidemic cases than has been reported in the literature. The reason for the failure to find the rash has probably been due to the lack of a careful search for it, to an error in calling the lesions capillary hemangiomata, or to the advanced stage of the disease process.
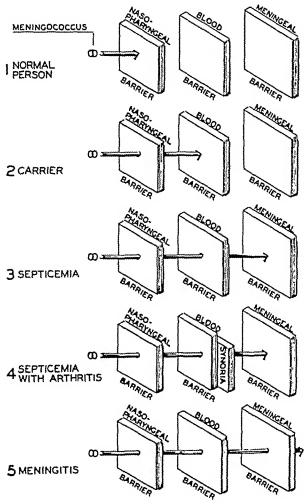
FIG. 1.—The path of infection of the meningococcus and the resistance offered by different individuals.

The specific rash of meningococcemia is always hemorrhagic (Fig. 2) and cannot be obliterated by pressure. A prodromal maculopapular rash may precede the petechial eruption but this is not characteristic. The eruption, if it is going to appear, invariably becomes manifest before the end of the first 24 hours of infection. Ordinarily, the rash is sparse and may be readily overlooked. The ankles and wrists probably

constitute the best locations to look for the rash as these areas are normally free of other types of skin eruptions. Any or all parts of the skin surface, the mucous or serous membranes may be involved. In our series, hemorrhages have been seen on the bridge of the nose; on the hard and soft palates; on the palms and soles; and in the con-
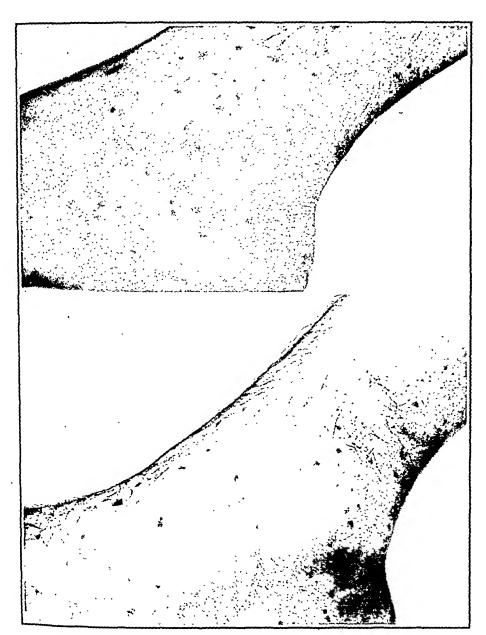
FIG. 2.—Petechiæ about the ankles of a soldier with meningococcemia.

junctivæ, in addition to the usual sites. Characteristically the rash reaches its full development within a few hours and fades rapidly, completely disappearing within a few days and leaving only a faint brownish discoloration of the skin. The lesions vary in size, shape and color. The majority of them are about 1 to 3 mm. in diameter, and range in shade from a rose color to a deep red. Not infrequently the

petechial spot is surrounded by a small red macule of a lighter color. In general, there should be no difficulty in differentiating these lesions from small capillary hemangiomata. In the very severe cases, purpuric spots (Fig. 3) or even large ecchymoses may accompany the petechiæ. These are usually of dark purple to blue-black color and vary considerably in size and shape. Although a widespread petechial and purpuric eruption usually occurs in the more severe cases, the absence of a rash does not necessarily indicate a mild case.

Rarely will the hemorrhagic form of measles be confused with meningococcemia, because the other associated clinical signs will make the diagnosis apparent. Typhus fever and Rocky Mountain spotted fever present a more difficult differential diagnosis. The severe meningococcemia may so closely simulate these two diseases as to be indistinguishable from them until meningeal signs become evident.
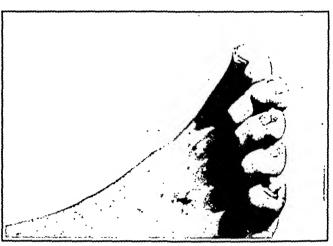
Fig. 3.—A large purpuric spot and several petechiæ on the dorsum of the foot of a soldier with meningococcic meningitis.

The other signs and symptoms of meningococcal sepsis, although less characteristic than the rash, are none the less important. The sudden onset of the disease, frequently in less than 6 hours, in an otherwise normal healthy individual, is an almost invariable feature of this type of infection. The chills, fever, drowsiness, headache, pallor, and pains in the limbs should suggest a blood stream infection. In many instances, the dissemination of the infection to the nervous system is so abrupt following the initial blood stream invasion, that a preliminary stage of sepsis fails of recognition. Signaling the spread of the infection to the nervous system are a series of signs and symptoms which hardly need enumeration. Perhaps the earliest sign is the severe intractable headache. In 99% of some 243 cases of meningococcal meningitis collected by the Surgeon General's office, headache was a primary and outstanding complaint. Of our cases, 94% have had this symptom as a chief complaint. The headache is generally felt all over

the head but is most severe in the frontal and occipital regions. Unrelieved by any form of treatment, including lumbar puncture, the headache has been justly described as "bursting." Vomiting occurs with more than average frequency. If present, it is very suggestive of central nervous system disease, especially when of a projectile nature. Disturbances of consciousness range from mild drowsiness to extreme coma. The drowsiness is not infrequently superseded by periods of marked irrationality. Other signs of meningeal irritation follow promptly, nuchal rigidity being the most readily recognized. The Kernig and Brudzinski signs soon become positive. Incontinence of urine and feces is common in the markedly irrational individuals. Rarely are the more advanced signs such as opisthotonus, and pareses of the cranial nerves seen because of the prompt administration of the sulfonamides.

Herpes simplex is frequently observed on the lips, nose, ears and back of the neck. This may occur any time after the 3d day and is seldom of any concern.

Of the 92 cases in this series, 30 were recognized before there were clinical signs of meningeal involvement. Spinal punctures were performed in 20 of these, and cells ranging in number from 8 to 27 were noted in 4 cases. Cultures of 3 of these fluids were positive for *Neisseria intracellularis*. Forty of the 90 blood cultures were positive for *Neisseria intracellularis*. Meningococci were grown from both the blood and spinal fluid in 23 instances. Seven cases of arthritis were encountered, 3 associated with meningeal involvement, and 4 without. The specific organism was grown from the synovial fluid in one patient with meningococcemia and arthritis, even though the blood culture was sterile.

Ability to diagnose meningococcic infections in the stage of sepsis will vary in different series of cases and in the same series of cases dependent upon: (a) the promptness with which medical care is sought; (b) the type and virulence of individual strains; and (c) the resistance offered by the nervous tissue of the individual. The history and physical findings alone should serve in establishing a diagnosis of meningococcemia and meningococcic meningitis. Laboratory confirmation should be sought in all instances, but treatment must not be withheld for this reason. Delay of 24 hours may mean the difference between treating a blood stream infection and a blood stream infection complicated by involvement of the central nervous system.

Summary and Conclusions. 1. An understanding of the pathogenesis of meningococcus meningitis is essential in order that the significance of its early signs may be appreciated.

2. Sufficient emphasis has not been placed upon the diagnostic value of the petechial rash in meningococcic infections.

3. Seventy-six out of 92 cases (82%) of meningococcic infections at this Post had petechial eruptions. In 5 instances a maculopapular rash was noted preceding the typical hemorrhagic eruption.

4. As the characteristic rash usually appears during the septicemic stage, its recognition will enable the early diagnosis of the disease.

5. In a number of instances the preliminary stage of sepsis may fail

detection as the dissemination of the infection into the nervous system is often very rapid.

6. Meningococcemia and meningococcic meningitis may occur in the absence of the characteristic rash.

REFERENCES

1. BRINTON, D.: Cerebrospinal Fever, Baltimore, Williams & Wilkins Company, 1941.

2. CRASTER, C. V., and SIMON, H.: J. Am. Med. Assn., 110, 1069, 1938.

3. HERRICK, W. W.: J. Am. Med. Assn., 71, 612, 1918.

4. HERRICK, W. W.: in Cecil's Textbook of Medicine, Philadelphia, W. B. Saunders Company, p. 192, 1937.

5. LONG, P. H.: Circular Letter No. 119, WD, Oct. 9, 1942, Services of Supply, Office of The Surgeon-General, Washington, D. C.

6. SMITHBURN, K. C., KEMPF, G. F., ZERFAS, L. G., and GILMAN, L. H.: J. Am. Med Assn., 95, 776, 1930.

MENINGOCOCCEMIA

By EUGENE P. CAMPBELL, M.D.*

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PHILADELPHIA, PA.

(From the University of Pennsylvania School of Medicine)

DURING the past four decades at least 88 case reports of meningococcemia have appeared in the American and British literature. This clinical syndrome first described by Soloman[54] and subsequently by Herrick,[29] Dock,[19] Morgan,[40] Graves et al.,[25] Appelbaum[1] and others is characterized by a long-standing intermittent fever, cutaneous rash, arthralgia, myalgia, headache and the presence of the meningococcus in the blood stream. This paper is a clinical report of 3 new cases and an analysis of 85 cases collected from the literature that fall into the confines of the group of prolonged cases in which we are interested.

Pathogenesis. The clinical group of infections caused by the meningococcus has increased during the past half century, from a single clinical syndrome, meningitis, to several clinical entities. The carrier state, nasopharyngitis, endocarditis, arthritis, meningococcemia, in addition to meningitis, show the extent to which the various tissues of the body are susceptible to this organism. In spite of the attention paid to the discovery of the various infections caused by this organism, we are not yet in a position to set forth a complete story of the pathogenesis of meningococcal infections. The controversy still prevails regarding such a fundamental feature as the route of invasion. The "direct extentioners" and the "blood streamers" have not completely settled their differences. Finding the organism in the nasopharynx and in the exudate at the base of the brain led to the conclusion that the most direct route of entrance was along the nerves. Others[13] have demonstrated potential perineural pathways and by analogy with staphylococcal, streptococcal and pneumococcal meningitis following sinusitis have assumed the same chain of circumstances for meningococcal infections. There is some support for this idea in the report of

* Currently with the Coordinator of Inter-American Affairs, Division of Health and Sanitation, Washington, D. C.

Embleton[22] who found that 32 out of 34 persons dying of meningococcal meningitis had empyema of the sphenoidal sinus. In 3 of these instances the meningococcus was found in the bone.

As early as 1907, Flexner[23] noted that the same basal type of exudative process developed at the base of the brains of monkeys even though the meningococcus was introduced into the lower spinal canal. This fact led him to feel that the theory of direct extension was invalid if based on proximity alone. A few years later,[23] however, he favored the direct extension route. Elser and Huntoon[21] summarized the problem up to 1909 and concluded by supporting the blood streamers. Herrick[29] divided meningococcal sepsis into three stages: the local infection in the nasopharynx, the general invasion of the blood stream and finally the metastatic localization in the various organs of the body.

The usual narrow localization of the meningococcus on the posterior wall of the nasopharynx in the region of the pharyngeal tonsil has often been noted; the non-observance of this fact has caused many a carrier survey to fail. Buddingh[8] has admirably demonstrated the various stages of the meningococcal infection in the developing chick embryo. Virulent meningococci after being engulfed by white blood cells have been shown to cause phagocytolysis (breakdown of phagocytes) due to meningococcal toxins with subsequent liberation of the organisms.[42] These facts have caused us to reëxamine the mechanisms surrounding the portal of entry which might bear on the problem of the route of invasion.

The secretory activity of the mucous membranes tends to wash the organisms from the nasal cavity into the pharynx. If a foothold is gained in the region of the pharyngeal tonsil the organisms may cause a local inflammation and hyperemia. If they permeate the mucous membranes and enter the lymphatic system they will meet the lymph node barrier and eventually reach the superior vena cava. Should they be engulfed by the white cell phagocytes, often found on the outer surface of the mucous membrane, and phagocytolysis occur after the white cells have reached the blood, the living organisms would be virtually injected into the blood stream. There are no fluid drainage tracts which normally operate from the nasal cavity and especially the posterior nasopharynx directly into the central nervous system.

Furthermore there are many reports of recovery of the meningococcus from the blood before meningitis sets in, many also in which meningitis never occurs. In certain instances of fulminating infections a greater number of organisms have been found in the lateral ventricles of the brain than in the spinal fluid,[49] a fact not easy to explain if one believes in the direct extension theory. It has been shown that meningitis can be produced in rabbits by intravenous injections of meningococci following the production of hyperemia of the meninges[2] and also following spinal drainage.[62]

The gradual accumulation of experimental evidence may eventually settle this important problem. At the present time, however, in view of the uncertainties, one can only say it appears likely that the usual route of invasion is by way of the blood stream.

Case Reports. The introduction of chemotherapy has resulted in important changes in the methods of treating this type of infection. The following case reports illustrate certain aspects of chemotherapy in meningococcemia.

CASE 1. J. C., a 20 year old white Civilian Conservation Corps enrollee, was admitted to the Walter Reed General Hospital on March 21, 1939, with the complaint of intermittent chills, fever and general malaise of 2 weeks duration. This patient had had a generalized ichthyosis of moderate degree throughout his life. His past history was not important. No physical abnormalities were noted other than the ichthyosis simplex and a skin rash. Scattered over the arms, forearms, legs and thighs were pink maculopapular lesions about 1 cm. in diameter. These areas were tender and seemed to be more numerous on the parts of the body least affected by the ichthyosis. His blood culture was positive for Group I-III meningococcus 9 days after admission. Sulfapyridine was started at once and during the succeeding 11 days the patient was given 41.6 gm. He made a prompt recovery with no complications after an illness of 7 weeks. No change in the ichthyosis was noted as a result of the chemotherapy.

CASE 2. T. K., an 18 year old white Civilian Conservation Corps enrollee, was transferred from a civilian hospital to the Walter Reed General Hospital on February 17, 1939. One month prior to this date, the patient had been admitted to the civilian hospital with meningococcal meningitis. He was promptly treated with antimeningococcus serum with excellent results and prompt recovery. He was just about to be returned to duty when he began having joint pains, a low grade intermittent fever and a generalized rash "similar to insect bites." No other physical abnormalities were noted, the heart was normal and there were no murmurs. He presented no evidence of meningitis. Three successive blood cultures were positive for Group I-III meningococcus. He suffered daily temperature elevations with chills until 2 days after sulfanilamide was started when he became afebrile and made a prompt recovery. He received 37 gm. of sulfanilamide in 9 days. The duration of this patient's illness was approximately $7\frac{1}{2}$ weeks.

CASE 3. W. P., a 17 year old white Civilian Conservation Corps enrollee, was admitted to the Walter Reed Hospital on June 7, 1938, with the complaint of a headache, fever and weakness of 2 weeks duration. It was learned that he had had meningococcic meningitis in February of 1938, was treated with serum and recovered without complication. He had enjoyed good health until 4 days prior to this when he complained of a fever and, for the first time, noted the presence of a macular rash.

Physical Examination. The patient was not acutely ill. The temperature was 98.8° F., the pulse rate 88 and the respiratory rate 20. His throat was injected and his tongue was coated. A red macular rash was observed on his feet, ankles, legs, thighs, buttocks and dorsum of the forearms. The early lesions were red, slightly elevated, round, regular, discrete and blanched on pressure. The older lesions were more elevated, had purple hemorrhagic centers which would not blanch on pressure. Some of the lesions were crusted. There were no scratch marks. The heart and lungs were normal. The blood pressure was 120 systolic and 68 diastolic. The spleen was not palpable and no other physical abnormalities were noted.

Laboratory Data. The initial blood examination showed 4.1 million red blood cells; 80% hemoglobin and 30,600 white blood cells (88% neutrophils). Blood Wassermann and Kahn reactions were negative. Agglutinations for Rocky Mountain spotted fever, brucellosis and tularemia were negative. A blood culture made on the 3d day, using an enriched medium, was strongly positive for Group II meningococcus. The first negative blood culture was obtained 19 days after admission.*

Course. The first 22 days of this patient's illness were characterized by daily paroxysms of fever, chills, crops of petechial spots and generalized arthralgia. Sulfanilamide in 1 gm. doses, 4 times a day, was started on the 4th hospital day and, though the patient continued to have fever, the rash disappeared until the 8th hospital day. He was desensitized to antimeningococcus serum and given 20 cc. intravenously. Additional serum was administered as indicated in Chart I but without beneficial results. Sulfanilamide was again tried in 25 gr. doses, 4 times a day for 4 days. The blood concentration reached 7 mg. per 100 cc. On the 4th day his red blood count had fallen to 2.7 million and the drug was discontinued. His temperature returned to normal on the 30th day of his illness and, after several weeks of convalescence he recovered without sequelæ. A total of 71 gm. of sulfanilamide and 195 cc. of antimeningococcus serum was used in the treatment of this patient.
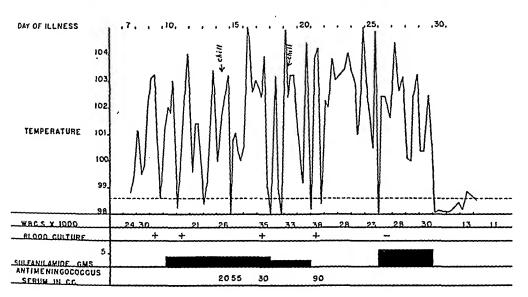
CHART I.—Case 3.

Clinical Characteristics of 88 Cases of Meningococcemia. This analysis of 88 cases, which includes the above 3 case reports, attempts to glean from the literature a more precise average clinical picture of this syndrome, as well as a better appreciation of some of its variations. Cases selected for this study were chosen on the basis of the prolonged course and the recovery of the meningococcus from the blood. There are a few reports in which the syndrome was identified after the eventual onset of meningitis and the subsequent recovery of the organism from the spinal fluid. In 3 cases described by Krumbhaar and Cloud,[32] and not included in this analysis, with sudden onset of meningitis, meningococci were isolated from the spinal fluid and meningococcic vegetative endocarditis was found at autopsy.

Of the 88 patients, 60 (69%) were males, 20 (33%) of whom were in the age group 20–29 years. The age distribution of 85 patients is presented in Table 1 using the age distribution of the population of the United States under 70 years for comparison. The exact age was not indicated in 3 case reports.

It will be observed that in the third decade the number of cases is nearly twice as great as one would expect. This difference is significant

and it might be interpreted to mean that persons in this age group are more liable to have meningococcemia than at any other age. This idea is strengthened by the fact that the two adjacent age groups also have higher relative incidences than might be expected. Nevertheless, I think this conclusion can only be advanced as a tentative one until more information is obtained.

TABLE 1.—AGE DISTRIBUTION OF 85 CASES OF MENINGOCOCCEMIA

Age groups	No. of cases	% of cases	% of U. S. population under 70—1930 census
0–9	8	9	20 3
10–19	19	22	19 8
20–29	27	32	17 4
30–39	15	18	15 4
40–49	12	14	12 7
50–59	3	4	8 9
60–69	1	1	5 5
Total	85	100	100 0

The duration of the illness from the onset of symptoms to cure was estimated in 80 case reports. The average duration was 11.2 weeks with extremes of 2 weeks and 120 weeks. In general, the younger the patient the shorter was the duration. An attempt to determine the seasonal prevalence of this disease was attended by little success. In 46 case reports the month and day of admission to the hospital were the only accurate dates obtainable, and if they are used the monthly prevalences are as follows: July, 7 cases; March and November, each 5 cases; January, February, June, September and December, each 4 cases; August and October, each 3 cases; May, 2 cases; and April, 1 case. It is to be noted that the duration of illness before admission to the hospital, the year of the attack, geographic location and the possible direct relation to epidemics of meningococcal meningitis were not taken into account.

TABLE 2.—FREQUENCY OF OCCURRENCE OF VARIOUS SIGNS AND SYMPTOMS IN 88 CASES OF MENINGOCOCCEMIA

	Male patients—60	Female patients—28	Total patients—88
1. Fever	57	25	82
2. Rash	53	25	78
3. Arthralgia	39	16	55
4. Chills	30	18	48
5. Headache	28	12	40
6. Myalgia	16	6	22
7. Arthritis	8	4	12
8. Vomiting	6	4	10
9. Palpable spleen	6	4	10
10. Sore throat	6	3	9
11. Sweating	7	2	9
12. Weakness	5	2	7
13. Herpes	4	1	5
14. Epistaxis	1	3	4

The frequency with which the various signs and symptoms occurred is shown in Table 2. Certain liberties were taken in the interpretation of a few reports. "Generalized aches and pains," for example, were

interpreted as arthralgia and myalgia in reports where these latter terms were not used. "Joint pain" was interpreted as arthralgia. "Swollen, tender joints," or "swollen joints" were classified as arthritis,[50] and tonsillitis or pharyngitis as sore throat.

Fever, rash, arthralgia, chills and headache constitute the five important features of this disease. Sore throat which might be expected to occur frequently, because of the portal of entry, was noted only 9 times. An enlarged spleen was recorded 10 times. The infrequent occurrence of herpes labialis was a bit surprising considering how often it occurs in acute meningococcal meningitis. Furthermore, 4 out of the 5 cases of herpes occurred in males, and all patients with this sign were in the third decade of life. In general, the frequency of occurrence of the subjective symptoms was lower in the first as compared with the later decades. Arthralgia, for example, was recorded only twice in 8 patients (28%) under 10 years of age, whereas it was noted 13 times in the 19 patients (68%) of the second decade.

In an earlier study[10] rash was noted as the most common feature. Several authors in the past 5 years have been specific in denying the presence of a rash. In 10 case reports out of the total (11.4%) there was no mention of a rash. This, I believe, is an important and encouraging change which supports the idea that blood cultures should be repeatedly made in all instances of obscure fever. As time advances it is conceivable that the symptom complex for meningococcemia will have rash in the third or fourth place.

The characteristics of the rash varied from a sparse petechial eruption to a diffuse one that commonly recurred in crops. The individual lesions varied in size from minute "flea bite" petechiae to papules 1 to 2 cm. in diameter. White centers and subsequent suppuration were rarely noted. The most frequent lesion was a small pink papule with a red center located chiefly on the chest, arms and legs. The purpuric or suggillation type of rash so frequently seen in the fulminating types of meningococcal infection was not noted in the prolonged and chronic forms. Richter, Harrison and Abernethy, Brown[47] and Appelbaum[1] have published good photographic reproductions of the rash.

Generalized aches and pains in the joints and back are prominent features of this disease. Often these symptoms appeared only at the time the patient was having an elevation in his temperature, subsiding during the afebrile intervals. These symptoms occasionally caused the physicians to make an initial diagnosis of rheumatic fever, and salicylates were often given only to find that the fever was of an intermittent type even following the full doses ordinarily employed in rheumatic fever. In these reports a search for malaria plasmodia in the blood was frequently noted because of the similarity of the fever variations to a tertian or quartan type, and quinine was occasionally given on an empirical basis.

Meningitis occurred as a complication in 25 patients. A point of considerable importance is the relationship between meningitis and fatality. Riven and Appelbaum[48] regarded meningitis as a bad prog-

nostic sign. Appelbaum[1] and Vesell and Barsky[60] were of the opinion that the presence of this complication does not make the outlook more serious. Chalier, Giraud and Morel[11] studied 27 cases of meningococcemia. In 8 cases without meningitis there were 4 deaths; in the remaining 19 cases with meningitis there occurred 6 deaths. They concluded that the localization in the meninges is favorable and helps the body to rid itself of the general infection. Among the 25 patients in the present report who developed meningitis there occurred 6 deaths; only 4 deaths occurring in the 63 patients without meningitis. This represents a statistically significant increase in the fatality in the meningitis group which fact would place some reliability upon the presence of this complication as an unfavorable prognostic sign. All patients developing meningitis who were over 39 years of age died (5 patients). Only 1 death occurred among the 20 patients with meningitis under 39 years of age (Table 3). It seems therefore that not only is meningitis a bad prognostic sign but the outlook is most serious when meningitis occurs in the older age groups. In 5 instances meningitis occurred before the prolonged meningococcemia set in. One patient had two separate attacks. Meningitis as a complication occurred most frequently between the 5th and 10th weeks of illness. Table 4 gives the frequency with which other complications occurred.

TABLE 3.—MENINGITIS OCCURRING AS A COMPLICATION IN 25 PATIENTS WITH MENINGOCOCCEMIA

Age groups	Male		Female		Total		Fatality (%)
	No.	Fatal	No.	Fatal	No.	Fatal	
0–9	0		2		2		0
10–19	2		1		3		0
20–29	10	1	2		12	1	8 3
30–39	2		1		3		0
40–49	2	2	2	2	4	4	100
50–59	1	1	0		1	1	100
Total	17	4	8	2	25	6	

Endocarditis was a complication which did not lend itself well to statistical study because of the indirect nature of the evidence presented as diagnostic of this condition. No uniformity of opinion exists as to the *in vivo* diagnosis of endocarditis caused by the meningococcus and postmortem evidence is scanty.[32] It seems most probable that the septicemic stage precedes both meningitis and endocarditis; consequently, in certain instances it is difficult to draw a line between the more characteristic cases of endocarditis and meningococcemia. It is believed that when vegetative endocarditis does set in as a complication of meningococcemia, the characteristic clinical picture of alternating periods of well-being with periods of indisposition, arthralgia and bouts of fever is changed. The patient whose condition is eventually proven to have been meningococcal endocarditis usually presents a symptom complex similar to the following: an intermittent fever which changes to a continuous one, this change being associated with the onset of weakness, loss of weight, congestive failure, cardiac incompetence, anemia and death.[32,46] In this group of 88 patients, 13 (15%) were

thought by their respective physicians to have had endocarditis, 4 of them died.[19,27,31] Necropsies were performed in 2 of these fatal instances and no endocarditis was found.[19,31]

TABLE 4.—FREQUENCY OF OCCURRENCE OF VARIOUS COMPLICATIONS AND ASSOCIATED CONDITIONS IN 88 CASES OF MENINGOCOCCEMIA

	Cases		Cases
Meningitis	25	Hemiplegia	1
Endocarditis	13	Thrombophlebitis	1
Nephritis	8	Jaundice	1
Anemia	6	Polycystic kidney	1
Pneumonia	2	Diabetes	1
Epididymitis	2	Congenital ichthyosis	1
Pericarditis	1	Banti's disease	1
Multiple abscesses	1	Conjunctivitis	1

Orgain and Poston[44] report an extraordinary coincidence of meningococcemia, pericarditis, pneumonia and thrombophlebitis in one patient. Two impacted wisdom teeth were extracted and this was followed by swelling of the neck and later fever and dull substernal pain. Sulfanilamide was administered with partial recovery until 15 days after the tooth extraction when the patient was readmitted to the hospital. Meningococci were recovered from his blood stream and pericardial fluid. He was treated with sulfanilamide and serum and after an illness lasting 68 days recovered without sequel.

Nephritis was reported in 8 patients, 5 of whom were in the first two decades of life. The nephritis was of the acute glomerular type. One patient[47b] died of nephritis 6 months after recovering from meningococcemia. The authors who reported this case believed there was some obscure causal relationship between the meningococcemia and nephritis. Anemia so frequently observed in other types of septicemia was noted only 6 times in this study and, in at least 1 of these 6, it was due to chemotherapy.

Heinle[27] describes the illness of 1 patient who had two well-defined and proven attacks of meningococcemia 2 years apart. This patient died in the second attack from "causes probably unrelated to the meningococcic septicemia." Cirrhosis of the liver, nephrosclerosis, bronchopneumonia and hemorrhage into the cerebellum were discovered at necropsy.

The treatment of meningococcemia has undergone important changes since the advent of chemotherapy. It is very difficult to make a true analysis of the curative effect of the various agents because of the tendency to use combined methods and also due to wide variations in amounts employed. Only those cases are being considered here in which no treatment, serum, or one of the sulfonamide derivatives was used. From Table 5 it will be seen that there is no significant difference between the no treatment group and the serum group. If, however, the serum group (46 cases) is compared with the whole chemotherapy group (14 cases) the difference in fatality is highly significant.

A total of 10 deaths (11%) occurred among the 88 patients. The 3 deaths not accounted for in Table 5 occurred as follows: 1 following treatment with antitoxin, sulfanilamide and blood transfusions;

another following the use of transfusions alone; the third after treatment with serum, emetine and mercurochrome. If the first death is credited to the chemotherapy group (15 cases) and the third credited to the serum group (47 cases) the difference in fatality is still significant.

TABLE 5.—RESULTS OF TREATMENT IN 68 PATIENTS WITH MENINGOCOCCEMIA

Method of treatment	Cases	Deaths	Fatality (%)
1. No therapeutic agent used	8	2	25.0
2. Serum alone	46	5	10.9
3. Sulfanilamide alone	6	0	
4. Sulfapyridine alone	7	0	
5. Sulfadiazine alone	1	0	
Total	68	7	

The 20 patients not included in Table 5 were treated with various combinations of the following therapeutic agents: antimeningococcal serum, antitoxin, blood transfusions, normal horse serum, autogenous vaccines, sulfanilamide, sulfapyridine, emetine, mercurochrome, hexamethylenamine, and fever therapy.

Reactions to antimeningococcal serum were frequent and in certain instances very severe. These reactions varied greatly from marked hypersensitivity to mild serum sickness. In several instances recovery seemed to follow the febrile reaction to the serum. Baehr's[3] patient had suffered from meningococcemia for 3 weeks. Immediately after the intravenous injection of 0.1 cc. of antimeningococcal serum the patient's temperature rose to 106.4° F., remained at this level for about an hour, and then returned to normal. The patient promptly recovered after this episode.

The average dose of selected therapeutic agents is given in Table 6. Vomiting complicated the treatment of 1 patient with sulfapyridine. An anemia resulted from the use of sulfanilamide in Case 3 above.

TABLE 6.—THE AMOUNT OF SELECTED THERAPEUTIC AGENTS USED IN THE TREATMENT OF MENINGOCOCCEMIA

Therapeutic agent	No. of patients	Average total dose	Extremes
1. Antimeningococcal serum	18	281 cc.	15-630 cc.
2. Sulfanilamide	5	56 gm.	16-148 gm.
3. Sulfapyridine*	3	26 gm.	16-34 gm.
4. Sulfadiazine	1	54 gm.	

* A fourth patient received 350 gm. of sulfapyridine.

The meningococcus was cultured from each of the 88 patients but not always without difficulty. Frequently several blood cultures were made before the organisms were recovered. With the steady improvement in our cultural methods as a result of a better understanding of the organism's growth requirement,[16] more and more cases are being diagnosed in the early stages. The organisms from 14 patients were typed, 6 were Group I–III and 7 were Group II–IV, 1 was described as of the "normal" type[18]—possibly, but not necessarily, Group I–III.

There are two important aids to the diagnosis of this condition. The first and most important is to think of meningococcemia whenever a patient presents a clinical picture characterized by prolonged inter-

mittent fever, rash, arthralgia, chills and headache. The second is the routine employment of frequent blood cultures made with enriched media.[16a] Stott and Copeman[57] state, "We believe that chronic meningococcal septicemia is so characteristic that bedside diagnosis is simple." Kennedy[31] makes the following observation: "Given a case of erythema nodosum, suspect meningococcus infection."

Summary. 1. As indicated by this analysis of 88 cases, meningococcemia is characterized by the following signs and symptoms in order of their frequency of occurrence: a long-standing intermittent fever, a polymorphous rash, arthralgia, chills and headache.

2. Meningitis occurring as a complication in meningococcemia, particularly in the older age groups, is associated with an increase in fatality and is believed to be a sign of bad prognosis.

3. The most favorable results from treatment were obtained by the use of chemotherapy.

REFERENCES*

1. APPELBAUM, E.: Am. J. Med. Sci., 193, 96, 1937.
2. AUSTRIAN, C.: Bull. Johns Hopkins Hosp., 29, 183, 1818.
3. BAEHR, G.: J. Mt. Sinai Hosp., 7, 294, 1941.
4. BENNETT, A. E., PERSON, J. P., and SIMMONS, E. E.: Arch. Phys. Ther., 17, 743, 1936.
5. BINNS, F., and CLANCY, J. J.: Am. J. Dis. Child., 57, 404, 1939.
6. BINNS, J. F., and FOTHERGILL, L. D.: New England J. Med., 205, 536, 1931.
7. BLOEDORN, W. A.: Am. J. Med. Sci., 162, 881, 1921.
8. BUDDINGH, G. J., and POLK, A. D.: J. Exp. Med., 70, 485, 1939.
9. CABOT, R. C.: New England J. Med., 201, 139, 1929.
10. CARBONELL, A., and CAMPBELL, E. P.: Arch. Int. Med., 61, 646, 1938.
11. CHALIER, J., GIRAUD, P., and MOREL, M.: J. de méd. de Lyon, 7, 565, 1926.
12. CLARK, F. B.: California and West. Med., 34, 361, 1931.
13. (a) CLARK, W. E. le G.: Report on Public Health and Medical Subjects, No. 54, pp. 1–27, 1929. (b) TURNER, A. L., and REYNOLDS, F. E.: Intracranial Pyogenic Diseases, London, Oliver & Boyd, 1931.
14. CONKLIN, C. B.: M. Ann. Dist. of Columbia, 4, 313, 1935.
15. CRAVEN, E. B.: South. Med. and Surg., 101, 367, 1939.
16. (a) Diagnostic Procedures and Reagents, New York, Am. Pub. Health Assn., 1941. (b) BRANHAM, S. E.: Bact. Rev., 4, 59, 1940.
17. DINGLE, J. H., THOMAS, L., and MORTON, A. R.: J. Am. Med. Assn., 116, 2666, 1941.
18. DINISON, S. B.: Lancet, 2, 424, 1938.
19. DOCK, W.: J. Am. Med. Assn., 83, 31, 1924.
20. EDMUNDSON, F.: Hahnemann Monthly, 67, 106, 1932.
21. ELSER, W. J., and HUNTOON, F. M.: J. Med. Res., 20, 377, 1900.
22. EMBLETON, D.: Brit. Med. J., 1, 7, 1920.
23. FLEXNER, S.: (a) J. Exp. Med., 9, 1942, 1907; (b) J. Am. Med. Assn., 69, 639, 721, 817, 1917.
24. FRIEDMAN, J. J., and BUCHANAN, J. A.: New York State J. Med., 39, 1662, 1939.
25. GRAVES, W. R., DULANEY, A. D., and MICKELSON, I. D.: J. Am. Med. Assn., 92, 1923, 1929.
26. HAYES, M. G.: Northwest. Med., 40, 284, 1941.
27. HEINLE, R. W.: Arch. Int. Med., 62, 575, 1939.
28. HENNELL, H., and WIENER, H. J.: Med. J. and Rec., 131, 292, 1930.
29. HERRICK, W. W.: Arch. Int. Med., 23, 409, 1919.
30. KATTWINKEL, E. F.: New England J. Med., 224, 685, 1941.
31. KENNEDY, J. C.: J. Roy. Army Med. Corps, 47, 6, 1926.

* Some of the references are to cases employed in the analysis but not cited in the context.

32. KRUMBHAAR, E. B., and CLOUD, J. H.: J. Am. Med. Assn., 71, 2144, 1918.
33. KRUSEN, F. H., and ELKINS, E. C.: Proc. Staff Meet., Mayo Clin., 12, 324, 1937.
34. LAMBIE, C. G.: Med. J. Australia, 25, 105S, 1938.
35. LEMANN, I. I., and TEASLEY, H. E.: New Orleans Med. and Surg. J., 83, 448, 1931.
36. MARLOW, F. W., JR.: J. Am. Med. Assn., 92, 619, 1929.
37. MASTER, A. M.: J. Am. Med. Assn., 96, 164, 1931.
38. MAXCY, K. F.: J. Infect. Dis., 23, 470, 1918.
39. MILLS, S. D., and SANFORD, A. H.: Med. Clin. North America, 18, 573, 1934.
40. MORGAN, H. J.: Bull. Johns Hopkins Hosp., 38, 245, 1921.
41. MOSS, G. C.: Med. J. Australia, 28, 548, 1941.
42. MURRAY, E. G. D.: Med. Res. Council, No. 124, London, 1929.
43. NEERGAARD, A. E.: Med. Clin. North America, 9, 461, 1925.
44. ORGAIN, E. S., and POSTON, M. A.: Am. Heart J., 18, 368, 1939.
45. RIDEN, V. B.: U. S. Navy Med. Bull., 28, 357, 1930.
46. (a) RHOADS, C. P.: Am. J. Path., 3, 623, 1927. (b) BANCKER, E. A.: J. Med. Assn. Georgia, 19, 480, 1930. (c) CECIL, R. L., and SOPER, W. B.: Arch. Int. Med., 8, 1, 1911. (d) WARFIELD, L. M.: Univ. of Pennsylvania Med. Bull., 16, 180, 1903.
47. (a) RICHTER, A. B.: J. Am. Med. Assn., 102, 2012, 1934. (b) HARRISON, F. F., and ABERNETHY, T. J.: Clin. Misc., Mary I. Bassett Hosp., 1, 3, 1934. (c) BROWN, C. L.: Am. J. Dis. Child., 27, 598, 1924.
48. RIVEN, S. S., and APPLEBAUM, A. A.: Ann. Int. Med., 4, 1387, 1931.
49. (a) RUNDLE, C.: Ker's Infectious Diseases, London, Oxford Press, 1929. (b) BRINTON, D.: Cerebrospinal Fever, Baltimore, Williams & Wilkins Co., 1941.
50. SCHEIN, A. J.: Arch. Int. Med., 62, 936, 1938.
51. SEELEY, S. F.: Mil. Surg., 71, 309, 1932.
52. SILVERTHORNE, N., and CAMERON, C.: J. Pediat., 19, 618, 1941.
53. SIMONSON, J. T., and TARNOWER, S. M.: J. Am. Inst. Homeop., 28, 67, 1935.
54. SOLOMAN, H.: Klin. Wchnschr., 39, 1045, 1902.
55. STEWART-WALLACE, A. M.: Brit. Med. J., 1, 931, 1936.
56. STOTE, C. L.: Lancet, 2, 701, 1929.
57. STOTT, A. W., and COPEMAN, W. S. C.: Lancet, 1, 1116, 1940.
58. THOMPSON, J. L.: Virginia Med. Monthly, 63, 240, 1936.
59. TOP, F. H., and YOUNG, D. C.: J. Michigan Med. Soc., 37, 528, 1938.
60. VESELL, H., and BARSKY, J.: AM. J. MED. SCI., 179, 589, 1930.
61. WATSON, L. D.: New England J. Med., 225, 685, 1941.
62. WEED, L. H., WEGELFORTH, P., AYER, J. B., and FELTON, L. D.: Monographs of Rockefeller Inst., No. 12, pp. 1–145, 1920.
63. ZENDEL, J. F., and GREENBERG, D.: New York State J. Med., 37, 1744, 1937.

THE HYPERKINETIC DISEASES

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NOSOLOGICALLY, maladies in which the cause is reasonably clear may be broadly classified into five groups: (1) congenital abnormalities of tissue or of chemical metabolism; (2) diseases of endocrine origin; (3) the deficiency diseases; (4) others resulting from exogenous factors (something foreign, a toxin, a trauma, a bacterium, for instance, has invaded the organism resulting in disordered anatomy and function); (5) the hyperkinetic diseases which are predominantly endogenous in nature. In this group, the maladies arise largely conditioned by psychosomatic factors, the result of the impact of environmental influence upon a constitutional background. In these diseases there is a primary exaggeration of normal functions while marked anatomic changes follow. It has hitherto been difficult to recognize that disordered function may sometimes precede morphologic changes, because of the hitherto

domination of the Continental School which taught that morbid anatomy precedes changes in function. The concept of hyperkinesis is important for the interpretation and integration of a group of maladies whose etiology is conventionally regarded as uncertain or unknown. Furthermore, these diseases are increasing rapidly, as hospital morbidity statistics eloquently testify; and, because of their prolonged and recurring nature, contribute in a large measure to the increasing cost of sickness.

In order to elucidate this thesis, we shall consider some of the normal body functions and try to show how their exaggerated trends represent the dominant expression of certain well-recognized diseases and, how, with the initiation of the hyperkinesis, there results an orderly biologic progression of the disease from a larval to the fully fledged type.

1. *Normal Intra-arterial Pressure.* Its exaggerated phase is hypertension of the greater and pulmonary circulations. In this report we shall refer only to hypertension of the greater circulation. In a recent publication,[32] I discussed the currently recognized causes. These are arranged in what I regard as the order of frequency: (1) psychologic; (2) persistent Graves' syndrome; (3) renal; (4) adrenal blastomata or paraganglioma; (5) congenital peripheral resistances;* (6) increased intracranial pressure; (7) carotid sinus; (8) lead poisoning; (9) Cushing's syndrome; (10) obesity. Of these, all but the hypertension arising from the first two factors represent processes in which morbid anatomy precedes the exaggeration of function. In the first two, *i. e.*, hypertension of psychologic origin and that occasionally following persistent Graves' syndrome, the hypertension represents the primary process in the sense that it is the earliest clinical manifestation, so-called "essential" hypertension. Elsewhere[33] I have detailed the factors that condition the initiation. Physically, hypertensive individuals tend to be soft muscled, unathletic in type and bodily movement, pudgy, short-necked, ungraceful and overweight. There is a definite relation between obesity and hypertension.[17] Psychically, they are the antithesis of the child in mental makeup. They do not play, they are irritable and have single-track minds without avocations. While their mental horizon is narrow, within this range they are tense and pursue their aims with a grim desperation. That heredity is a factor in the production of hypertension has been well attested,[40,51] but in how far the hypertensive constitution is genotypic or phenotypic is still problematical. No one can deny that there has been a definite increase in essential hypertension in recent decades, as the present appalling mortality from the cardiovascular-renal syndrome testifies. I have elsewhere[33] discussed the influences that have brought about this increase. Briefly, I believe they may be explained, at least in part, as a by-product of modern civilization, of the stresses and strains that modern living entails. Testimony for this statement is the strik-

* The use of this phrase having been questioned, the author replies: "I purposely used the term congenital to include the cases of congenital stenosis of the aortic isthmus."—EDITOR.

ing increase in modern times of hypertensive disease in the northern negro,[25] whereas in his native habitat in the heart of Africa, hypertension is unknown.[15] It probably is not diet, because diet, except in so far as it is high caloric, does not induce hypertension. Moreover, the diet of northern negroes has not changed. It cannot be climate because this has not varied. I suspect that the reason may be industrialization and the competitive forces of modern civilization.

In other words, essential hypertension of the greater circulation, like infection and other disease conditions, is the resultant of a background and an insult. Either factor alone is insufficient.

The ultimate anatomic consequences of essential hypertension of the greater circulation are familiar—arteriosclerosis and eventually the catastrophic evidences of the cardiovascular-renal syndrome. The sequential relation of hypertension to arteriosclerosis and its attendant anatomic phenomena has been questioned, because the decrescent or senile type of arteriosclerosis occurs even without hypertension. These observers forget that hypertension is not an absolute but a relative value and that it is merely an exaggeration of the normal intravascular tension which by itself, given sufficient time, will produce arteriosclerosis. The evidence for this point of view lies, as I have pointed out,[34] in the independence in incidence between arteriosclerosis of the greater and lesser circulation. Gross arteriosclerosis of the pulmonary artery occurs almost exclusively in conditions in which a hypertension of the pulmonary circuit can be predicated, such as mitral disease, emphysema, etc. Now inasmuch as the normal pulmonary pressure is only one-sixth that of the aorta, the probability is very strong that even under extreme conditions, the pressure in the pulmonary circuit never approaches the normal pressure in the systemic circuit. The conclusion is obvious that if pressures less than the normal aortic pressure can produce arteriosclerosis in the pulmonary circulation, the normal systemic pressure, given sufficient time, can produce the decrescent or senile type of arteriosclerosis of the greater circulation. The following equation was therefore suggested to cover some of the factors: arteriosclerosis = intravascular pressure × time. There are, it is true, secondary conditioning factors involved in the genesis of arteriosclerosis, for instance, the chemical composition of the blood, the vascular supply of the walls of the vessels, intravascular stresses and perivascular resistance;[32] but these factors merely modify the lesion and affect its distribution. Apparently, normal intravascular pressure is the only normal function that has been shown to give rise to anatomic and sometimes to actual clinical disease. In this sense, arteriosclerosis (at least anatomic but not necessarily clinical) is the inevitable destiny of all animals who have a vascular system such as our own (Chart I).

This chart explains why visceral arteriosclerosis even though patchy in its distribution is only exceptionally single in its clinical manifestations.

Inasmuch as the principal process disturbed in Graves' disease is the basal metabolic rate, we shall discuss the syndrome more fully under that functional heading. At this time, we need only point out

that hypertension of the greater circulation is one of the possible sequences of uncured or spent Graves' syndrome. In the earliest phases, the systolic pressure is usually elevated with a low diastolic pressure, probably due to the shunt engendered by the enormous increase in vascularity of the thyroid gland.[7] If the malady persists, these pressures no longer are labile and become more or less fixed. Eventually, both systolic and diastolic pressures rise and, in the course of many years, the cardiovascular-renal syndrome arises in one or more of its manifestations. It has been my fortune to have observed this sequence of events in a considerable number of instances, especially in older patients afflicted with persistent Graves' disease. Page[11] describes a syndrome, usually occurring in young women with essential hypertension, characterized by a high-strung temperament, tremor, tachycardia, perspiration, slight enlargement of the thyroid gland, sensitivity to cold and a slightly elevated basal metabolism, which he believes is due to diencephalic stimulation. His description certainly fits that of Graves' syndrome and I suspect that this disease is the cause of their hypertension. Inasmuch as I have tried to show (*v. i.*) that Graves' disease is largely a personality disease, the psychogenic origin of some cases of essential hypertension cannot be ignored. The fact remains that Graves' disease may occasionally be followed by the same clinical sequelæ as those of essential hypertension.

CHART 1.—POSSIBLE ANATOMIC AND CLINICAL SEQUENCES

Normal tension ⎱ Arterio-
Hypertension ⎰ sclerosis

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Brain (cerebral arteriosclerosis; apoplexy).
Retina: retinopathy.
Heart: coronary disease; arteriosclerotic valvular disease; myocardial insufficiency
Pancreas: capillary fibrosis of islands of Langerhans (diabetes).
Splanchnic arteriocapillary fibrosis.
Kidney: arteriocapillary fibrosis; nephrosclerosis.
Extremities: arteriosclerotic gangrene.
General arteriosclerosis; cachexia; atrophy.
}

2. *Basal Metabolic Rate.* The disease in which hyperkinesis, *i. e.*, increased basal metabolic rate, is a dominant expression is Graves' disease.

In a previous paper[35] I tried to show that Graves' disease is not a nosologic entity in the sense that it has a consistent background in morbid anatomy and a clear etiology, but rather a series of disorders arranged in a biologic progression that have received different eponyms in the past. The natural history of the disease usually extends over a long period. The earliest phase has been called Basedowid, autonomic imbalance, pre-Basedow, neurocirculatory asthenia,* etc. The middle

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* There has been much debate whether "neurocirculatory asthenia" is the earliest stage of Graves' syndrome. We have records of at least a dozen cases at the Mt. Sinai Hospital where at first admission the diagnosis of neurocirculatory asthenia was made, and at second admission Graves' syndrome, in both instances on conventionally recognized criteria. Furthermore, on regression of the Graves' syndrome, a residuum of signs and symptoms often persists that is indistinguishable from neurocirculatory asthenia. As this exposition proceeds, we shall see the close relation of both to states of fear, whether in war or civil life. In a subsequent communication this topic will be discussed more fully.

stage has been termed "formes frustes," while the final stage is that conventionally termed "Graves' disease" with the characteristic quadrad of symptoms, *i. e.*, tremor, tachycardia, enlarged thyroid gland and exophthalmos, plus an elevated basal metabolic rate. Between the larval and the final florid form, one finds various combinations of signs and symptoms. For these reasons, the term "Graves' syndrome" is regarded as preferable. The proof of this statement lies in the fact that not only are such forward transitions frequently observed but, more frequently, regressions to the larval phases under the influences of either spontaneous remissions or of treatment.

I believe it is a fallacy to regard hyperthyroidism, as measured by the basal metabolic rate, as synonymous with Graves' syndrome. Graves' syndrome contains many clinical elements that are not explainable by the elevated basal metabolism alone. To regard the measurement of the basal metabolic rate as the sole diagnostic test of Graves' syndrome is arbitrary and not warranted by clinical facts for the following reasons: (1) Patients with so-called "spent" or "burnt out" Graves' syndrome who reveal the typical quadrad of signs may possess a basal metabolic rate within the normal range. (2) After a subtotal thyroidectomy which usually reduces the basal metabolic rate to normal, many of the clinical manifestations may persist for years, even though the patient is economically and perhaps socially restored.* (3) During the larval phases the basal metabolic rate is usually normal; but when, under the influence of an emotional strain, the disease assumes the florid form with a rise in the basal metabolic rate, are we justified in saying that a different disease has been born? All we may say is that hyperthyroidism has entered the picture. (4) The administration of toxic doses of thyroid gland mimics but by no means completes the clinical picture of Graves' syndrome. There is elevation of the basal metabolic rate, tremor and tachycardia and perhaps loss of weight but no exophthalmos or swelling of the gland. (5) Cases with clinical evidences of Graves' syndrome associated with myxedema occur rarely.[30] These mostly represent exhaustion phenomena. Hyperthyroidism as measured by the basal metabolic rate may be regarded as a sign, probably the most important of Graves' syndrome and as a measure of the activity of the disease, comparable to fever in infections. When the temperature of a patient with typhoid fever returns to normal, he has not necessarily lost his disease.

The common denominator in these various phases is a characteristic personality. In no disease that I am aware of is the personality so indissolubly bound with the clinical manifestations as in Graves' syndrome.

If the patient has been well observed before the onset of the disease or if his personality is reconstructed afterward, he will be found to conform to a vast race that may be described in general as the sensitive,

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* It is occasionally an exceedingly difficult problem to estimate what is meant by "cure" in Graves' syndrome. In my experience, it is exceptional to get a complete *restitutio ad integrum* in this disease. One or a number of the original quadrad of signs and symptoms usually persist.

emotional type; furthermore, this personality persists no matter what treatment is instituted, although clinical evidences of the disease have been eliminated. I regard the personality of the patient with Graves' syndrome as so characteristic that, in doubtful cases, the elucidation of the personality serves as a diagnostic measure. Phlegm and Graves' syndrome are, in my experience, antagonistic. Occasionally, one observes patients who appear to have a phlegmatic temperament but when one digs deeper, one finds that it is only a mask.

There are no anthropologic signs that are characteristic of the disease. However, in the constitutional phase these patients present, as a rule, a number of physical signs which represent the larval phases of the future characteristic quadrad of signs. Their eyes stare and are bright and they show more of the whites, especially in action or under emotional stress. During emotion, also, the pulse rate rises to excessive heights and there is tremor. In women, the neck tends to be fuller than normal and under emotional strain, especially during menstruation, when women are usually more touchy, they confess that their throats are larger. Their basal metabolic rate while within the normal range, usually, in my experience, veers to the plus side. Dermographia is nearly always present. These people are exceedingly touchy and respond to their environment like an Æolian harp. A look or harsh word upsets them easily and often irretrievably. As a consequence, they are usually intolerant. They are shy and introvert and live a life of escape. Their personalities have an unusual manic-depressive trend, sometimes even to the edge of a psychosis. They are quick in their movements and mental process. They are prolific day dreamers and idealism plays a large rôle in their mental life. They show a leaning toward the mystic and reveal the artistic temperament, so that in this group one frequently finds poets, writers, painters. Charm is a salient characteristic. They are usually bad sleepers. In my experience, they respond badly to thyroid preparations as opposed to those of phlegmatic temperament. They commonly relate that in their childhood a nervous disorder followed a slight emotional upset, such as a recitation or school examination. They tire easily mentally and physically. They are sensualists and live on stimulation, emotional, physical and even chemical. They easily become drunkards or drug addicts; indeed, suicides are by no means uncommon. These patients belong to what Kretschmer calls the "cyclothymic" constitution.

In no disease is a study of the immediate family so illuminating. The same malady afflicts two or more members of the family more than the normal law of averages allows and, what is particularly significant, few of the siblings are adjusted and phlegmatic. Most suffer from various forms of neuroses, and manic-depressive trends are common.[6] In how far these tendencies are genotypic or phenotypic, I am not prepared to say but from the study of numerous families, I believe that environmental influences, especially overprotection, play the dominant rôle.

In the majority of instances, the onset of the fully fledged disease is

ushered in by a psychic insult for which the patient was more or less unprepared, for instance, a robbery, a fire, the death of a close relative, an unrequited love affair, a terrible confinement, a frightful sexual episode, a sudden economic loss, an unwanted pregnancy, are some of the insults that I recall. There was a sudden crop of cases of Graves' syndrome in Vienna after the theatre fire horror in 1884 and in San Francisco after the earthquake. We have been particularly struck in the Mt. Sinai Hospital with the frequency of Graves' syndrome in German refugees, so that the term "Hitler Graves" has come into vogue. The essential ingredient in this insult is fear. Less often, the disease arises from slow and reiterated insults and the transition between health and disease is indefinable. At times after a sudden shock, the malady reaches its fruition even within a few days.

If the opportunity arises to observe the development of the malady in a person whom the physician has previously known, he will note that the disease represents an exaggeration and fixation of previous trends. A pulse that was normally fast, especially under an emotional stimulus, beats faster. The wide eyes become exophthalmic; a tremor which was previously noted only under excitement becomes exaggerated and constant and the previous emotionalism and instability of temperament is intensified. The basal metabolic rate is now definitely elevated.

This sensitive, emotional personality accounts for a number of things that have interested students of the disease: (1) The greater preponderance of Graves' syndrome in the female. (2) The rarity of the disease in children, in whom the subtler emotive powers are not fully developed. (3) The rarity of the disease in primitive races or in those of crude fiber. As in hypertensive disease, there has been in our experience at the Mt. Sinai Hospital, a decided increase of the disease in northern negroes since they became sensitized by contact with the white race. (4) The rapid increase in Graves' disease in recent decades owing to the increased "strain of living," the resultant of increased protective mechanisms.[36]

The psychogenic background of Graves' syndrome also explains the freedom of the lower animals from this disease because civilization has not affected them. Indeed, the complete disease cannot be experimentally reproduced—only individual signs and symptoms. The instances in which it has been reported are of doubtful validity. Graves' syndrome is essentially a human disease and especially one of the higher civilizations.

Some years ago, Lorand and Moschcowitz[28] published a psychoanalytic interpretation of Graves' syndrome. They found that: "already in childhood their adjustment to the members of their family was unsuccessful. On the one side they were too much pampered by the parents, especially by the mother, and on the other side, too great a demand was put upon them in the course of their development to which they could not adjust themselves as a result of their earlier protective environment. The vast majority of such patients may be said to have been sensitized to life. They were so shielded in their

childhood that when they reached adult age they could not face the conventional tribulations of every-day life with equanimity. They had difficulty in making decisions upon ordinary matters and were infantile in their reaction to life. There was a continual escape from every-day realities and, in consequence, these people would aver that their life had been an unusually hard one. The relation in childhood to the siblings as illustrated in certain cases is even carried over to adult life; for instance, the older sister replaces the father or mother to the other children. In their adult environment they showed the same type of emotional reactions to the attachments and frustrations as they did in childhood. Sexual difficulties, degrees of maladjustment, frigidity in women, fear of pregnancy and fear of childbirth combined with intense resentment and repressed aggression against men were present in all the patients. The unmarried girls showed a type which we can describe as psychosexual infantilism. Their childish attitude about sex matters, their more or less abnormal reactions and feelings concerning their menses, their attitude concerning marriage and sex in general lack all the judgment of the normal adult.

"Their relation and their reactions to their employers show an exact parallelism to their early reactions to their parents. The traces of their earlier emotional fixation to the parents were so obvious in their adult attitude to society that it could not be overlooked.

"In the male patients, whether married or unmarried, the same situations exist. Degrees of sexual impotentia, or at least difficulties in their sexual adjustment, were always present. The masturbation of puberty was continued by some of them up to marriage, partially on account of fear concerning sexual infection and partially as a result of their difficulties in their adjustment to the other sex. Coitus interruptus in the married patients was practiced for a long period of time to meet the demands of their wives in order to prevent impregnation, and at the same time, this sexual dissatisfaction caused resentment against the sexual partner. It then resulted in a tendency to stay away from intercourse or a strong drive toward unfaithfulness, with implications of fear and feelings of guilt."

The recognition of the individual and his environment is fundamental in the therapy of the disease. The human equation remains no matter what therapy is undertaken, and the impact of the two constitute a potential for a recurrence of the disease. It is futile to discharge a patient after a subtotal thyroidectomy without taking into consideration the ability of the patient to meet the ordinary stresses of every-day life and the environment to which he returns. Indeed, the lesson taught by these recurrences is that the treatment of the patient begins only when the operation has been finished. Although the constitution and the environment appear essential in the mechanism of production of Graves' syndrome, there must be another factor or at least a compensating mechanism, for the reason that sometimes one observes patients in whom despite the presence of both these factors, a Graves' syndrome did not develop.

When the disease is full blown to the stage of so-called toxic goiter

and continues more or less fixed, there may be a number of eventualities. We have already referred to the possibility of a progressive hypertension and its potentialities. In addition, the persistent tachycardia or the onset of a cardiac arrhythmia, especially auricular fibrillation, may result in myocardial insufficiency. Finally, of course, the disease may lead to death with the symptoms of acute thyrotoxicosis, namely, tachycardia, vomiting, diarrhea, progressive elevation of bodily temperature, emaciation and acidosis.

CHART 2.—CLINICAL EVALUATION OF GRAVES' SYNDROME

Constitution → formes fruste → Graves' syndrome ⎰ Persistent tachycardia / Arrhythmia; auricular fibrillation ⎱ →Myocardial insufficiency

⎰ Hypertension / Acute thyrotoxicosis ⎱ See Chart 1

Synonyms: Basedowid. Autonomic imbalance. Pre-Basedowid.

3. Normal Gastric Acid and Secretion. The exaggerated phase is hypersecretion and hyperchlorhydria. The disease in which hyperchlorhydria is most often associated is peptic ulcer.

The cause or causes of peptic ulcer are obscure, but the view is steadily gaining ground that in the background is a constitution that represents a combination of physical and psychogenic characters. The physical characters have been described by Draper.[16] They have the "lean and hungry look" of Cassius, the expression is hard and tense, the eyes deep and sullen, the lines of the face are sharply drawn, the mouth is firm, the jaws sharply angled and the masseter muscles are prominent. These patients are usually cyanotic and show a tendency to erythremia. To what extent these physical characters are phenotypic or genotypic is as yet impossible to estimate.

Psychologically, in my experience, the vast majority of ulcer folk conform to a certain type of personality. They are intolerant, all or nothing, self-absorbed and mentally inelastic folk with strong aggressive, masochistic and sadistic tendencies. They harbor strong grudges and it takes them long to overcome any emotional strain. Even their humor is sadistic. They have a paranoid trend. They are haters and fighters.

As in Graves' syndrome, one finds with remarkable frequency that preceding the onset of the clinical symptoms, the patient passed through a period of emotional conflict; the illness or death of a relative, economic distress, the development of a powerful hate, etc. Whether this actually initiates the ulcer or merely activates it, is problematical; more likely, the psychologic insult induces activity. Clinicians have long recognized that a restful holiday can induce a remission even without the conventional dietary regimen. It has been my experience that when a patient is resistant to the Sippy treatment, he is often in a state of mental upheaval; when this is corrected, the symptoms promptly abate.

Indeed, so strong are the interweavings between the psyche and peptic ulcer that a considerable lore has accumulated on the psycho-

genic origin of peptic ulcer. I have summarized these views,[37] but the conclusions are diverse and conflicting. Experimentally, peptic ulcers analogous to those found in the human organism have been produced in animals but only by methods that do not obtain in human beings. Experimentally, the vast majority of observers have succeeded in producing only acute hemorrhagic erosions and because they show no tendency to be limited to the "pathway" and invariably heal promptly, it is unlikely that they represent the forerunners of the true human peptic ulcer. Indeed, the entire issue concerning the pathogenesis of peptic ulcer has been clouded by the uncritical acceptance of the hemorrhagic gastric erosion as the precursor of peptic ulcer. Hemorrhagic erosions are common phenomena at postmortem and are found in association with true peptic ulcer, in sepsis, in peritonitis following abdominal operations[19] in localized sclerosis of a gastric vessel, and following operations upon the brain,[13] but proof as yet is not forthcoming that these erosions, any more than the experimental variety, pass into the true Cruveilhier peptic ulcer. As Mann and Bollman[29] state bluntly, "If the mucosal lesion in man which precedes the development of the characteristic peptic ulcer begins as a hemorrhage into the mucosa, it appears that many of the results of our investigations (v. i.) would have little if any clinical bearing." Indeed, a considerable part of the experimental research concerning the problem of peptic ulcer has concerned itself with attempts to transform this acute hemorrhagic erosion into the chronic type; the results at best are equivocal. A few have succeeded but by means that are unphysiologic, for instance, by repeated Roentgen ray dosages or by injecting chemical irritants in the neighborhood of the ulcer.

The recent clinical and experimental observations of Bernheim and Penner[44] who showed that hemorrhagic erosions of the gastro-intestinal tract are commonly shock phenomena, have helped I believe to clarify considerably our knowledge of the causes of hemorrhagic erosion both in man and animals. Their observations certainly make one skeptical of the much quoted neurogenic theory of the origin of peptic ulcer sponsored by Cushing,[13] who found that *operations* on the brain were occasionally followed by a gastric erosion. Penner and Bernheim call attention to the frequency of shock after such operations, and in their analysis of postoperative hemorrhagic erosions they also found that shock was a common feature. This probably accounts also for some of the erosions found in association with peptic ulcer with fatal hematemesis (Moschcowitz, Mage and Kugel[38]). The association of true peptic ulcer with erosion does not necessarily justify the conclusion that the erosion was the precursor of the ulcer. In addition to the fact that it may be a shock phenomenon from severe hemorrhage, it may be the result of the associated mucosal inflammatory changes secondary to the peptic ulcer. In brief, no satisfactory evidence has been presented which shows that the hemorrhagic erosion is the earliest phase of peptic ulcer. Hauser,[21] who had spent a lifetime studying the genesis and pathology of chronic peptic ulcer, doubts this relationship.

The mechanism whereby the impact of psychologic influences upon a constitutional makeup is transformed into a peptic ulcer has been subject to considerable speculation. Part of the difficulty arises from the fact that, as opposed to hypertension and Graves' disease, we are not in the position to observe transitions, either clinically or in morbid anatomy. Hitherto, the stomach has been clinically an inaccessible organ, the only method of visualization being the Roentgen ray. This method is hardly satisfactory for the purpose of studying natural history because it only demonstrates an ulcer after it has matured. Serial gastroscopy offers a reasonable hope that the earliest lesion of peptic ulcer and its transition may eventually be demonstrated.

The only experimentally produced ulcers that correspond closely to those of the human were produced by Mann and Bollman.[29] These ulcers not only occurred exclusively in the "pathway" but grossly and histologically were identical with the true peptic ulcer. They obtained their results in dogs by elimination of the duodenum with the jejunum sewed to the pylorus. If the common bile duct and the pancreatic duct remained implanted into the duodenum, they obtained 20% ulcers; if these ducts were transplanted into the ileum, they obtained 50%. If the entire normal mechanism for receiving the gastric contents was eliminated by the functional resection of the duodenum together with the secretion poured into it by the second method, with anastomosis of the proximal end of the jejunum to the terminal ileum, they obtained 95% ulcers. The controlling factor is the acidity. In other words, these methods prevent the neutralization, dilution or buffering of the gastric contents as it passes the stomach. By repeatedly giving hydrochloric acid to normal dogs by continuous drip 8 hours each day, they obtained an ulcer in about 4 weeks. Daily repetition of excess acidity depresses the neutralizing ability. Such ulcers heal in a few days following discontinuance of the acid. In the type of ulcer obtained by elimination of the duodenum and its contents, the ulcer appears rapidly, in hours or less than a day. The morbid anatomy of the primary lesion as given by Mann and Bollman probably represents the prototype of that which, we predict, will eventually be found in the human stomach. "Macroscopically, they appeared as saucer-like depressions in the mucosa about 2 cm. distal to the pylorus. In their incipience, there is always a ring of mucosa between the ulcer and the pylorus. In the earliest stages, there is a small area covered with a homogeneous gray membrane. When the membrane is sponged off, a slight depression is uncovered where the surface of the mucosa had disappeared and which bled profusely. After the mucosa is eroded the process may proceed quickly until the wall is perforated. Microscopically, the gray membrane is composed of mucosal cell débris. In the earliest stages the injury involves only the tips of the tubules. Hemorrhage then occurs between the tubules underneath the gray covering. As more of the mucosa is injured, leukocytic infiltration occurs, the ulcer penetrates beneath the muscularis mucosa and the ulcer assumes the chronic type.[37] Mann and Bollman have apparently solved the problem of chronicity of peptic ulcers, because the agency

which prevents their healing persists. These experimental results prove, if nothing more, that the acid factor is vital in the production of ulcer. This has long been surmised clinically by a number of significant observations: (1) Reports of simultaneous association of peptic ulcer and anacidity are so rare that experienced observers like Palmer and Heinz[43] are skeptical that this association exists. (2) Recurrence of either peptic or jejunal ulcers following gastric resection does not result, at least in our experience at the Mt. Sinai Hospital, if complete anacidity is obtained. (3) In the rare cases of ulceration of Meckel's diverticulum, aberrant gastric mucosa is nearly always present and the ulcer is found in the intestinal and not in the gastric portion of the mucosa.[3] (4) Peptic ulcer was not found in association with achylia gastrica in over 800 cases of pernicious anemia.[26]

In how far do these observations apply to the psychogenic origin of peptic ulcer? In view of the importance of the acid factor, the question arises whether the hyperchlorhydria and hypersecretion so commonly associated with peptic ulcer, especially of the duodenal variety, precede or only follow the initiation of the defect. That emotion may produce temporary hyperchlorhydria is a well-established observation.* There are no data available which indubitably establish the presence of hyperchlorhydria in the human previous to the development of an ulcer, but in view of Mann and Bollman's work on the acid factor and the fact that psychic influences cause an increase in acidity and secretion, the probability is strong that continued or reiterated emotional strains do cause a sustained hyperchlorhydria and hypersecretion before the initiation of the ulcer. It seems highly probable therefore that hyperchlorhydria and/or hypersecretion represents one of the intermediary mechanisms between the psyche and the ulcer. In this connection, the experiments of Stahnke[48] and Silverman[47] are convincing. Stahnke showed in dogs that electric stimulation of the vagus nerve, 40 minutes daily for 2 to 3 months, resulted in marked increase in gastric acidity and peptic activity and, in some instances, a peptic ulcer followed. Silverman found that sham feeding through an esophagostomy opening in the neck caused a powerful stimulation of the peptic glands with large amounts of fluid of a high acid and peptic titre, and eventually the occasional appearance of a peptic ulcer.

Although the discussion in the two following paragraphs is not directly related to the hyperkinetic aspects of peptic ulcer, it is necessary because in many quarters such mechanisms are seriously considered and would tend to negate our thesis.

There is a widely prevalent view that part of the mechanism of the development of peptic ulcer is vascular by way of the vasomotor nerves causing spasms,[4,21,50] or by narrowing (arteriosclerotic ulcer). Considerable argument and experiment has been expended upon this phase

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* In a recent publication, Hoelzel[22] who made daily observations upon his gastric acidity over a period of years, found that while he was passing through a period of fear owing to the anticipation of being shot, his acidity rose to appreciable heights. When he moved from his city so that the occasion for fear ceased, his acidity returned to normal.

of the problem, but it cannot be said that the results leave a sense of satisfaction. A vascular mechanism for the genesis of peptic ulcer will be difficult to maintain for the following reasons: (1) It is almost impossible to cause an infarct or necrosis in the stomach even by complete closure of a gastric vessel. This is manifest not only experimentally but also in human beings when it becomes necessary in the course of gastric operations to ligate numerous vessels. (2) There is no evidence that the sclerotic vessels so commonly found at the base of a peptic ulcer represent primary changes. They are probably secondary inflammatory lesions. Peptic ulcer is surely not a disease of the decrescent years when vascular occlusions in other parts of the body are common enough. (3) A vascular origin does not explain the remarkable predilection of peptic ulcer for the pathway and the upper duodenum. (4) If we accept the experimental ulcer of Mann and Bollman as the prototype of the human ulcer, there is nothing in their description of the pathogenesis of these ulcers that suggests a primary vascular mechanism. Indeed, as Palmer[42] points out, the fact that the lesion begins in the mucosa and not in the walls, speaks against a vascular mechanism.

Furthermore, the contention of Konjetsny and his school that a chronic gastritis precedes the development of a peptic ulcer must be viewed with much skepticism. Available evidence seems to show that in most instances the gastritis is secondary, the result of chronic infection from the ulcer. When a "gastritis" is present unassociated with ulcer, the histologic criteria, at least as far as I have observed, are remarkably indefinite both in regard to its status as a true inflammation and to its variations from the normal.* Other considerations aside, a primary gastritis does not explain the almost human character of peptic ulcer, its limited localization not only to the gastric and upper duodenal mucosa but more particularly, to the "pathway," its great preponderance in males and the rarity of the disease in childhood and in primitive peoples.[20] Even assuming that a gastritis may be the background, such an assumption adds nothing to the etiology of peptic ulcer, because the cause of the gastritis is still dark. The same processes of reasoning are applicable in relation to the problem as to whether bacteria, especially streptococci, are responsible for the lesion. In other words, every attempt to explain peptic ulcer as an infection has proven futile.

The relation of psychosomatic factors to the genesis and recurrence of peptic ulcers has significant implications not only on therapy but on prophylaxis. Hurst[23] has pointed out that peptic ulcer has taken the lead as the chief cause of medical disability in British and Canadian soldiers; and Crohn[11] believes, in view of Hurst's report and the rise of peptic ulcer in Finland, that we may expect a rise in the incidence of peptic ulcer in this country in the near future. It is our distinct

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* It seems a remarkable fact that the normal histology of the stomach has not been sufficiently studied either in regard to normal deviations, age, the active or resting stage, character of nourishment, race, etc.

conviction that there has been an increase in evidence of peptic ulcer in the Mt. Sinai Hospital, especially since the depression of 1929.

As I pointed out some years ago[37] there is a remarkable parallelism between peptic ulcer and Graves' syndrome. In both there is a rather characteristic psychic background, although at times these backgrounds seem to overlap. In Graves' syndrome, the psyche is a highly sensitive and emotional one; in peptic ulcer it is rigid, aggressive and intolerant. In both, a latent malady is brought to light by emotion, either catastrophic or by slow reiterated insults. In both, it is sometimes exceedingly difficult to know when the disease actually begins, but whereas in Graves' syndrome, if one is fortunate, the observer can follow the intensification and increasing tempo of the signs and symptoms from the larval constitutional stage to the formes fruste and finally to the fully blown form, in peptic ulcer, owing to present diagnostic criteria, one can never be sure whether the previously existing chronic indigestion represented an actual ulcer or not. Strictly speaking, therefore, we do not yet know the preceding or intermediate stage of peptic ulcer.*

In both, recurrences are common and frequently these recurrences are preceded by emotional upset. In both, excess of normal function dominates the clinical expression of the disease; in both psychic rest is an important adjuvant in therapy, and in both, surgical intervention has parallel indications and results. In Graves' syndrome the operation aims at removing the hyperthyroid element; in peptic ulcer, the elimination of the hyperchlorhydria and the hypersecretion.

4. *Tonus of Cardiac Sphincter.* The increased phase of this tonus is represented in cardiospasm. That there is a normal cardiac sphincter has been demonstrated by Hurst,[24] who has coined the term "achalasia" for the persistence of the normal tone of this sphincter which fails to open before the normal peristaltic esophageal wave in the act of swallowing. Cardiospasm may be primary or secondary. Secondary cardiospasm follows various lesions, for instance gastric or esophageal ulcer, gall bladder disease, gastric and esophageal neoplasms, etc., but more often cardiospasm is primary. It is needless to enumerate the various causes of primary cardiospasm that have been submitted, because they have not been substantiated by adequate evidence. Most of the hypotheses implicate overstimulation of the vegetative nervous system, either physiologic or as the result of organic changes in the plexus of Auerbach embedded in the walls of the esophagus. The probability is indeed strong that the cardiospasm is mediated through the pathways of the vegetative nervous system, but this is a mechanism and not a cause. Furthermore, it is very probable that the organic degenerative changes witnessed in the Auerbach plexus are not primary but secondary to the ever-present inflammatory changes involving the coats of the esophagus in prolonged cardiospasm. In

* It should be strongly emphasized that clinical peptic ulcer and peptic ulcer of morbid anatomy are by no means synonymous. It has been shown time and again that peptic ulcer of even considerable dimensions may exist without any clinical evidences whatever. A recurrence of symptoms may not represent the formation of a new ulcer but the activation of a preexisting one.

recent years, evidence has accumulated that primary cardiospasm is psychogenic in origin. The older textbooks all agree that cardiospasm usually occurs in psychoneurotics and that it frequently follows a psychologic trauma. Schindler[46] in his cases unearthed a history of deep anger a day or two before the onset of symptoms. Indeed, in the earliest phases of the cardiospasm he obtained a cure by psychotherapy or hypnosis. Alkan[2] found violent psychic excitement preceding the onset of symptoms. More recently, Winkelstein[54] reported 8 cases in all of which a psychologic trauma initiated the symptoms of cardiospasm.* In 2 of his cases, seen in the early phases, psychotherapy resulted in a cure. In the later phases when the cardiospasm is fixed and anatomic changes have occurred, both Winkelstein and Schindler agree that dilatation of the esophagus is essential.

The natural history of cardiospasm is fairly typical. In the early phases, the symptoms come and go with the intervals of well-being becoming progressively shorter. Eventually the difficulty in swallowing becomes constant, the dilatation and tortuosity of the esophagus become progressive and finally pronounced inflammatory and ulcerative lesions ensue with marked hypertrophy of the muscular coat. The intensification of the spasm and the presence of these organic changes account for the failure of psychotherapy in the terminal stages of cardiospasm.

Whether there is a constitutional factor or a characteristic psychologic pattern in patients with cardiospasm requires further observation.

5. *Tonicity, Peristalsis and Secretion of the Colon.* These three normal functions are grouped together because, as a rule, the clinical experiences consequent upon their hyperfunction are associated. The maladies in which these hyperfunctions predominate are mucous "colitis" and non-specific ulcerative colitis.

(a) *Mucous "Colitis."* For the following data I am largely indebted to the excellent comprehensive monograph of White, Cobb and Jones.[53] The term mucous "colitis" covers not only those conditions in which mucus is constantly passed but a number of conditions in which the passage of mucus is an occasional symptom. These have been described under the appellations of "irritable colon," "spastic constipation," "nervous diarrhea" and "alternating constipation and diarrhea." The malady occurs uncomplicated but is not infrequently associated with other psychosomatic disorders, such as the irritable heart of soldiers (neurocirculatory asthenia), asthma, Graves' syndrome and peptic ulcer. There is no crude correlation with any anthropomorphic type. The sigmoidoscopic picture, while not specific, reveals spasm, dilatation of the superficial venules, the presence of mucus and a somewhat granular appearance of the mucosa. The characteristic radiographic appearance of the colon reveals rapid filling, spasm and irritability, deep haustrations and the string sign. Little is known of its morbid anatomy because patients do not die of this disease. In

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* In the discussion of Winkelstein's paper, Verbrycke referred to a physician who was cured of a cardiospasm by dilatation of the esophagus. He remained well for months but had a prompt recurrence when bandits robbed his bank.

one case of Mallory's, the goblet cells of the mucosa secreted a large amount of mucus. The patients often reveal vasomotor symptoms mediated through the autonomic nervous system, such as dilation of the pupils, ptyalism or aptyalism, sweating, exaggerated pilomotor responses, sighing respiration and sphincter response. They report that allergy was the cause in only about 4%. In the remainder, emotional tension, acute and chronic, was the cause. Psychologically, White, Cobb and Jones found that asthenia was common. There was high incidence of sexual indifference, two-thirds of the women were frigid and men were satisfied with infrequent intercourse. Minor compulsions existed in a large number—excessive neatness, meticulousness and overconscientiousness. True obsessions were not encountered. These patients ruminated on their problems. Phobias were common, especially of crowds, and they have depressive tendencies. The majority were dependent persons. The emotions most commonly associated were resentment, fear and guilt in that order. They showed difficulty in making decisions. White, Cobb and Jones report experiments in which changes simulating those seen in mucous colitis were produced by drugs which mimicked the action of parasympathetic sacral outflow and the central theme of their exposition is the thesis that "mucous colitis is a physiologic disorder of the colon brought about through the action of the sympathetic nervous system," and that the commonest cause of parasympathetic overstimulation in mucous colitis is emotional tension. This tension was obviously present in 92% of the psychogenic cases in their series. The prognosis for cure is bad because the major emotional problems are usually insoluble. The treatment of such patients consists largely in mental hygiene, including insight, assistance in solving conflicts, social adjustments, disciplinary management, reassurance and transference, suggestion and resolution of the neurosis possibly by a Freudian analysis. In addition, symptomatic therapy may be helpful.

(b) *Non-specific Ulcerative Colitis.* Testimony is accumulating that it is a psychosomatic disease. It is tempting to regard non-specific ulcerative colitis as an advanced phase of mucous colitis or spastic colon but thus far the testimony of experienced gastro-enterologists[9,12,53] does not permit this conclusion. In my comparatively limited experience, there is no such intermediate clinical phase; the transition from apparent health to the clinical evidence of disease is abrupt. Nevertheless, in a considerable number of patients one can unearth a history that in childhood under the influence of emotional distress, the bowels moved at least 2 or 3 times. Sullivan[49] and Cullinan[12] noted this occurrence in a number of their patients with ulcerative colitis and, in others, a history of spastic constipation. Despite the apparent species difference, in non-specific ulcerative colitis as in mucous colitis, all the normal functions of this gut are exaggerated, upon which are superimposed the exudative manifestations of the inflammatory process.

Murray[39] was the first to emphasize the rôle of psychogenic factors in non-specific ulcerative colitis. He reported 12 cases. After com-

menting that a state of emotion is often accompanied by hypermobility, spasticity, hypersecretion and vasomotor disturbances, he believes that these disturbances can be transmuted into a physical condition, if the emotional conflict is deep seated or chronic, if there is a specific organism, or if the individual is predisposed by heredity, early training, etc. He found beside fearfulness, emotional immaturity in their mental make-up. Of 7 men, 6 were tied to their mothers and 1 substituted an elder sister for his mother. None were married. Of the 5 women, 3 were married, 1 to a man of her own age. The most frequent conflict arose from the mother attachment and the desire to get married. It is not so much the sudden fright but a new situation which keeps the patient in a state of constant apprehension. Their characters may be described as analerotic with masochism and sadism.

Sullivan[49] reported the psychiatric data on 15 patients. Many of the patients were neat and fussy. Ten patients showed an inability to throw off the effects of an emotional episode. Financial worries occurred in 8 of the 15 and sexual maladjustment was present in all but 2 cases. Five of the males showed abnormal attachments to the mother; in the remaining 5 there was an attachment to some close relative. There is an amazingly close chronologic association between emotional episodes and the onset of the diarrhea. In 11, the bloody diarrhea began within 48 hours of the upset. In the other 4, the emotional state was a prolonged one, but in this group the exacerbation of the diarrhea was as closely dependent on the emotional state as in the first group. Psychotherapy produced striking results when other methods failed.

Wittkower[55] regards ulcerative colitis as a disease of the mentally ill or maladjusted. Almost all of his patients showed character disorders, obvious neurosis or psychosis. He divides his patients into 4 groups: (1) the obsessional—those characterized by overconscientiousness, overscrupulousness, cleanliness and abstinence; (2) the hysterical—those characterized by emotional lability, temper, tantrums, childishness, self-centeredness and suggestibility; (3) a less well-defined group containing some schizothymics and depressives; (4) miscellaneous personality types. In 37 of 40 patients, the colitis or its recurrence was antedated by disturbing events. He also justifies psychotherapy in the treatment of the disease.

Daniels[14] studied 25 cases in the Constitution Clinic at the Presbyterian Hospital. Of 14 cases that were studied intensively comprising 2 men and 12 women, 8 showed a pathologic attachment to a relative; in 6, the death of this relative had been of paramount importance. Indecision concerning marriage was marked in 2 unmarried members of this group and in 2 others engagement and marriage were the precipitating causes. In 2 cases, the onset of symptoms was associated with childbirth, which also played a prominent rôle in another. Money difficulties were significant in 4 cases. He submits a detailed report of 3 patients. Good results are reported by psychotherapy.

From the psychoanalytic viewpoint, Alexander[1] contrasts the colonic type of patient as dependent, anal receptive and oral aggressive, in

contrast to the gastric ulcer type, characterized by "an inner rejection of passive receptive and oral aggression tendencies." Alexander stresses the symbolic use of feces as an expression of hostility, and sometimes as the equivalent of childbirth, an observation noted by Daniels in one of his patients.

In a study of 100 or more cases of non-specific ulcerative colitis in the Mt. Sinai Hospital, I have been strongly impressed by the psychosomatic relationship. As others have noted, there was a close relationship between the onset or exacerbation of symptoms and an emotional upheaval. Indeed, a psychosomatic study is part of the history of every case of ulcerative colitis admitted to the Mt. Sinai Hospital. Often the onset of symptoms was not occasioned by a catastrophic insult but by a prolonged conflict attendant upon a life situation into which the patient found himself propelled. The three dominant life situations that affected these patients were, in the order of frequency, parental fixation, marriage and money, not by any means always sharply demarcated but with interrelationships. Sexual maladjustments were common, as indicated by the frequency in which the onset occurred during and immediately after a honeymoon. There were no apparent anthropologic constitutions, nor was there any particular age incidence, although the majority occurs in the 2d and 3d decades. According to the pediatrists children below the age of 10 are rarely affected.

Psychologically, I have found that they are usually soft and non-aggressive, fussy and overconscientious, sensitive and immature, weak-willed, narrow horizoned and, as White, Cobb and Jones found in mucous colitis, altogether utterly dependent individuals. Like others, I have found that occasionally psychotherapy produces dramatic remissions of the disease, more likely in the early than in the chronic and advanced cases.

The mechanism whereby psychogenic influences produce this serious disease is entirely speculative. It is permissible to state that hyperkinesis is a predominant part of the mechanism and that it is mediated through the pathways of the vegetative nervous system. Experimentally, lesions simulating non-specific ulcerative colitis have not as yet been reproduced. To my view, the most promising lead for the interpretation of the mechanism is that of Lium,[27] who made explants of the colon in the abdominal wall. He showed that these explants react to various stimuli by a spastic contraction of the musculature with discharge of mucus and with hemorrhage and ulceration. These stimuli include mechanical stimulation, parasympathomimetic drugs, such as acetylcholine and prostigmine and dysentery toxin. It is conceivable that overstimulation of the vegetative nervous system produced by psychologic influences may produce the same effect as parasympathomimetic drugs. In this connection, it is interesting that White, Cobb and Jones produced changes in the rectal mucosa stimulating those observed in mucous colitis by the oral administration of acetyl-beta-methylcholine.

Hyperkinesis is well illustrated in the genesis of the psychoses; but

these differ from the forementioned hyperkinetic diseases in that, although the sequence from the larval to the labile finally into the fixed stage can be readily traced, morbid anatomic changes, at least thus far, have not been demonstrated.

6. *Manic-depressive Psychosis.* The exaggeration of function that this malady represents may be called the normal rhythm of life, in which the swings between ecstasy and depression are low and to which the average person readily adjusts himself. If one has known a patient intimately before the onset of a manic-depressive psychosis, one can invariably recall that the patient always possessed an abnormal excursion in his emotional range. Indeed, the constitution of the manic-depressive is almost identical with that of Graves' syndrome. The emotions pass from ecstasy to depression in rapid sequence; in fact, the incidence of manic-depressive psychosis in Graves' syndrome is by no means uncommon.[5] The patient is high-strung, deeply emotional, narcissistic, violent in his expressions and anxious. He belongs to the type of individual whom I have described as "allergic to life." This type, as I tried to show, is to a large extent the result of environmental influences dating from the earliest years of life, in most instances, maternal overprotection. But there must be a genetic component as well, because all psychiatrists are agreed that manic-depressive psychosis is commonly hereditary.[5,8] As in so many of the hyperkinetic diseases, the pronounced attack of manic-depressive psychosis and its prolonged fixation dates from a sudden emotional strain or prolonged mental conflicts. When the psychosis comes, the individual is not different but an exaggeration and fixation of his former self.

7. *Paranoia.* Paranoia may be regarded as an exaggeration of the normal effective state of the mind. My limited experience with patients whom I have known well and who have developed paranoia has afforded the conviction that I have been observing nothing more than exaggeration and fixation of personality trends. These folk have always been suspicious, eccentric and afflicted with profound obsessions. This impression is confirmed by the observations of experienced psychiatrists. Thus White[52] quotes Mangan as saying, "They show peculiarities during childhood, manifesting themselves in a certain taciturnity, moroseness or disinclination to associate with other children as freely as usual. The child may also have shown a tendency to make friends with an older person, stay at home and read and sew instead of play and may have a tendency to day dreams and the building of air castles." This period may be termed, according to the psychiatrists, the hypochondriacal stage; this is followed by the stage of persecution and finally by the stage of transformation of the personality. Church and Peterson[10] say that paranoia "affects by preference individuals who are even in their childhood, peculiar, morbid, shy, irritable, mistrustful and misanthropic." "Puberty and adolescence tends to intensify the morbid peculiarities already present." Braude[8] comments that from childhood, the make-up of the paranoic is egocentric, selfish, suspicious, proud and mystic; he is impatient and defiant of conventions. Sadler[45] says that paranoia develops in

persons who are suspicious, sensitive, jealous, as well as those who suffer from an inordinate ambition. Paranoid trends are also more likely to develop in shy, dreamy, selfish, prudish and impractical individuals. Sadler and Adolph Meyer[31,45] even speak of a paranoid constitution. All are agreed that heredity is a strong predisposing factor in paranoia. The mechanism whereby this type personality is transformed into a psychosis is not pertinent to our thesis, nor, indeed, is there any agreement on the part of psychiatrists. But at all events, in this psychosis as in the hyperkinetic diseases that we have discussed the transition can be traced from a basic constitution, conditioned by heredity, to a labile and finally to an intensification and fixation of symptoms.

I am quite sure that I have not exhausted the list of hyperkinetic diseases. For instance, I am confident that the tone of the bronchial musculature plays a rôle in certain forms of asthma of psychogenic origin and that persistent bronchial spasm and compensating phenomena lead to emphysema and eventually to hypertension of the pulmonary circuit and its cardiac sequelæ. Also, I have reason to believe that some forms of schizophrenia subscribe to this pattern. My purpose rather has been to submit a concept. The major problems in the study of the hyperkinetic diseases are two: (1) The mechanism whereby the impact of environmental influences upon a constitutional background bring about disease. Inasmuch as the hyperkinetic diseases are essentially human diseases, experimental methods to reproduce them have largely failed because they cannot introduce the human equation. (2) The determination of the reason why one function is predominantly involved. The concept of "organ inferiority" is thus far entirely speculative. The answer probably lies, as Dunbar[18] puts it, "in the various combinations of heredity and constitutional factors, specific conflicts in the course of development, and the total personality organization, plus adventitious factors." White, Cobb and Jones say, "It is not the objective fact of impact which is important but the way in which it is experienced." We may call attention at this point to the fact that there is no specificity between psychosomatic factors and the hyperkinetic function, the proof lying in the not infrequent association in the same patient of two hyperkinetic diseases and indeed of all aspects of psychosomatic medicine. In the solution of these problems the general practitioner possesses a decided advantage over those engaged in exclusive hospital practice because the latter see only a small cross-section, usually the terminal, of the life cycle of the disease. This limitation applies as well to the psychiatrist, although the latter is indispensable in the elucidation and interpretation of the background and the mental workings of the patient. What is needed is a balanced combination of all. It is encouraging that intensive study of the psychosomatic diseases has already been begun in the Psychosomatic Clinic at the Presbyterian Hospital in New York City and the Psychanalytic Institute in Chicago.

The maladies I have described have certain common denominators:

A. These diseases have as backgrounds a constitution which is usually both genotypic and phenotypic. The direct stimulus is a maladjustment either sudden or protracted to the trials and tribulations of modern civilized existence. These two factors may be compared as the tinder and the spark, analogous to what occurs in infection.

B. There is an exaggeration of function. It is well established that emotion even in the apparently normal being can cause an elevated blood pressure, rise in the basal metabolic rate, an increase in secretion and in the acidity of the stomach, an increase in the tonus of the cardiac sphincter and an increase in the peristalsis and increased secretion of the colon, and it is plausible to assume that if these emotional reactions continue and are profound enough that they may cause a fixation of the hyperkinesis. In all likelihood, this mechanism is mediated through the vegetative nervous system.

Curiously, the only psychosomatic disease I am aware of in which normal functions are depressed is that strange malady known as *anorexia nervosa.* This malady in its severe forms may be regarded as the expression of a wish to die or spiritual suicide. Patients hesitate to take their lives but reduce every item of living to the lowest possible terms. Clinically, though not etiologically and pathologically, it resembles Simmonds' disease and is characterized by profound loss in weight, a subnormal body temperature, a lowered basal metabolic rate, diminished sexual activity, amenorrhea, slow pulse, a lowered blood pressure and hypochlorhydria. Indeed, there are so many features that resemble hibernation, in which the pituitary gland represents part of the mechanism, that one wonders whether the difference between Simmonds' disease and anorexia nervosa consists solely in the fact that in Simmonds' disease the primary change in the pituitary gland is organic and in anorexia functional. The disease appears to be exquisitely psychogenic in origin, most often the result of excessive parental domination. In fact, the disease responds well to psychotherapy. At all events, it is a mystery why in this disease of psychosomatic origin so many of the normal bodily functions should be depressed instead of being elevated.

C. These hyperkinetic diseases are essentially human diseases and more particularly of civilization. There is ample testimony that they are rare or uncommon in primitive people and when they do occur in such folk, it is only when they are in competition with the white race. With the exception of peptic ulcer and then only rarely, these diseases have not been observed spontaneously in the lower animals. Nor, indeed, can these methods be satisfactorily reproduced experimentally except by methods that are unphysiologic in the human race.

D. These hyperkinetic diseases rarely occur before the age of puberty when the emotive faculties become more subtle and adjustment to life becomes more sensitive and complex.

E. These hyperkinetic diseases have an unusual tendency to recur. This is not to be wondered at when one considers that the disease is so closely allied to the ego, and how difficult it is to eliminate completely

a normal function of the body. Of all the functions that I have listed the only one that can be eliminated is gastric acidity. If an achlorhydria can be produced by subtotal gastrectomy, one can be assured that the patient will not have a recurrence of his peptic ulcer. In subtotal thyroidectomy for Graves' syndrome, one only removes part of the total metabolism for the thyroid gland is only responsible for 40% (Means[30]). Recurrence after operation for Graves' disease is always possible, first, because the personality remains, and, second, because complete adjustment to the old environment has not taken place. Essentially, the treatment of the patient really begins when the operation has been completed.

F. Inasmuch as the transition from the normal or static phase to the abnormal is subtle and the line of demarcation is indefinite, there can be no specific diagnostic tests for these diseases, only an arbitrary one. All bodily functions have ranges within the normal, not a precise mathematical quantity. The diagnosis of these diseases therefore depends upon a perspective of the composite picture, in which a study of the personality of the patient and his life history is a vital consideration.

As a rule, the hyperkinetic diseases evolve through 5 discernible stages: (1) the constitutional; (2) the exaggeration of function; (3) the lability of signs and symptoms; (4) the fixation of this exaggerated function; (5) somatic changes. In other words, the time factor is important in the genesis of these diseases. Relativity has its place in medicine as it does in physics.

Summary. The concept is submitted that certain diseases that may be called "hyperkinetic" represent primary exaggerations of normal bodily functions with morbid anatomic changes as a sequel, instead of the usually accepted reversed order of disease process. Tentatively, the following diseases are submitted: (1) Hypertension of the greater circulation, which represents an exaggeration of the normal intra-arterial pressure and leads to arteriosclerosis and the cardiovascular-renal syndrome. (2) Graves' disease, which represents, in greater part at least, an exaggeration of the normal basal metabolic rate. (3) Peptic ulcer, in which one of the dominant expressions is the exaggerated acidity and secretion of the normal stomach. (4) Cardiospasm, which represents an increase in the normal tone of the cardiac sphincter. (5) "Spastic colon," mucous "colitis" and ulcerative colitis, which represent exaggeration of the normal tonicity, peristalsis and secretion of mucus of the colon. (6) Manic-depressive psychosis, which represents an exaggeration of a normal rhythm. (7) Paranoia, which represents an exaggeration of the affective functions.

The biology of these diseases is discussed and possible mechanisms and new approaches are suggested. These maladies have certain common denominators. They possess a constitution that is usually a combination of phenotypic and genetic characters. The direct stimuli are maladjustments between the psyche and the environment. These diseases are essentially limited to the human species and are mostly products of civilization. Experimentally, they cannot be reproduced

in animals except by methods that are unphysiologic for human beings. They rarely occur before the emotive faculties are fully developed. They possess a remarkable tendency to recur. Because the transition from the normal to the abnormal is gradual, no specific diagnostic test is applicable, unless it is an arbitrary one. The diagnosis therefore must depend upon a study of the composite picture—the organ—personality. These diseases, as a rule, evolve through 5 stages: (1) constitution; (2) exaggeration of function; (3) a lability of signs and symptoms; (4) fixation of this exaggeration of function; (5) somatic changes.

REFERENCES

1. ALEXANDER, F.: Psychanalyt. Quart., **3**, 501, 1934.
2. ALKAN: Anatomische Organkrankheiten aus seelischer Ursache, Stuttgart, Hippocrate verlag, 1930.
3. ASCHNER, P. W., and KARELITZ, S.: Ann. Surg., **91**, 573, 1930.
4. ASCHOFF, L.: Lectures on Pathology, New York, 1924.
5. BARRETT, A. M.: Assn. Res. Nerv. and Ment. Dis., **3**, 248, 1923.
6. BAUER, J.: Die konstitutionelle Disposition zu innern Krankheiten, Berlin, 1921.
7. BOAS, E. P.: J. Am. Med. Assn., **80**, 1683, 1923.
8. BRAUDE, M.: Clinical Psychiatry, Philadelphia, The Blakiston Company, 1937.
9. BUZZARD, E. M., RICHARDSON, J. S, and TURNER, R. W. D.: St. Thomas Hosp. Rep., **3**, 55, 1938.
10. CHURCH, A., and PETERSON, F.: Nervous and Mental Diseases, 9th ed., Philadelphia and London, W. B. Saunders Company, 1921.
11. CROHN, B. B.: Edit., Am. J. Digest. Dis., **8**, 359, 1941.
12. CULLINAN, E. R.: Brit. Med. J., **2**, 1351, 1938.
13. CUSHING, H.: Peptic Ulcer and the Interbrain, Springfield, Ill., Charles C Thomas, 1932.
14. DANIELS, G. E.: New England J. Med., **226**, 178, 1942.
15. DONNISON, C. P.: Lancet, **50**, 6, 1929.
16. DRAPER, G.: Disease and the Man, London, Paul Trench, Trubner & Co., 1930.
17. DUBLIN, L.: The Influence of Weight on Certain Causes of Death, Human Biology, p. 170, May, 1931.
18. DUNBAR, H. F.: Emotions and Bodily Changes, 2d ed., New York, Columbia University Press, 1939.
19. EISELSBERG, A.: Arch. f. klin. Chir., **59**, 837, 1899.
20. HARTMAN, H. R.: Med. Clin. North America, **16**, 1357, 1933.
21. HAUSER, G.: Handb. d. spez. path. Anat. (Henke-Lubarsch), Berlin, V, Part IV, 1926.
22. HOELZEL, F.: Am. J. Digest. Dis., **9**, 188, 1942.
23. HURST, A.: Am. J. Digest. Dis., **8**, 321, 1941.
24. HURST, A.: Quart. J. Med., **23**, 491, 1929-30.
25. JAFFÉ, R. H.: Ztschr. f. allg. Path. u. path. Anat., **55**, 209, 1932.
26. KAHN, J. R.: Am. J. Med. Sci., **114**, 463, 1937.
27. LIUM, R.: Arch. Int. Med., **63**, 210, 1939.
28. LORAND, S., and MOSCHCOWITZ, E.: J. Nerv. and Ment. Dis., **79**, 136, 1934.
29. MANN, F. C., and BOLLMAN, J. L.: J. Am. Med. Assn., **99**, 1576, 1932.
30. MEANS, J. H.: Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937.
31. MEYER, A.: Theory and Practice of Psychiatry, St. Louis, C. V. Mosby Company, 1936 (quoted by Sadler, W. S.).
32. MOSCHCOWITZ, E.: Vascular Sclerosis With Special Reference to Arteriosclerosis, Oxford Press, 1942.
33. MOSCHCOWITZ, E.: J. Am. Med. Assn., **93**, 347, 1929.
34. MOSCHCOWITZ, E.: Am. J. Med. Sci., **174**, 388, 1927.
35. MOSCHCOWITZ, E.: Arch. Int. Med., **46**, 610, 1930.
36. MOSCHCOWITZ, E.: New England J. Med., **213**, 617, 1935.
37. MOSCHCOWITZ, E.: New England J. Med., **212**, 603, 1935.
38. MOSCHCOWITZ, E., KUGEL, V., and MAGE, S.: Am. J. Med. Sci., **202**, 52, 1941.
39. MURRAY, C. D.: Am. J. Med. Sci., **153**, 239, 1930.
40. O'HARE, J. P., WALKER, W. G., and VICKERS, M. C.: J. Am. Med. Assn., **73**, 27, 1924.
41. PAGE, I. H.: Am. J. Med. Sci., **199**, 8, 1935.

42. Palmer, W. L.: Psychanalyt. Quart., 3, 501, 1934 (quoted by Alexander, F.).
43. Palmer, W. L., and Heinz, T. E.: Arch. Int. Med., 53, 269, 1934.
44. Penner, A., and Bernheim, A. I.: Arch. Path., 28, 129, 1939.
45. Sadler, W. S.: Theory and Practice of Psychiatry, St. Louis, C. V. Mosby Company, 1936.
46. Schindler, R.: München. med. Wchnschr., 73, 1612, 1926.
47. Silverman, I. S.: Zentralbl.f. Chir., 54, 2385, 1927.
48. Stahnke, E.: Arch. f. klin. Chir., 132, 1, 1924.
49. Sullivan, A. J.: Am. J. Digest. Dis., 2, 651, 1936.
50. von Bergmann, G.: Berl. klin. Wchnschr., 56, 524, 1918.
51. Weitz, W.: Ztschr. f. klin. Med., 96, 151, 1923.
52. White, W. A.: Outlines of Psychiatry, Washington, 1932.
53. White, B, Y., Cobb, S., and Jones, C. M.: Psychosomatic Med. Monog. No. 1, Washington, National Research Council, 1939.
54. Winkelstein, A.: Trans. Am. Gastro-Enterol. Assn., 33, 137, 1930.
55. Wittkower, E.: Brit. Med. J., 2, 1356, 1938.

THE USE OF SULFAPYRAZINE IN INFANTS AND CHILDREN

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Studies of the absorption, excretion, and distribution of sulfapyrazine (2-sulfanilamidopyrazine) in adults have been reported by Hamburger, Ruegsegger, Brookens, and Eakin.[5] Comparison of studies on adults and on children receiving other sulfonamide drugs indicates that in the two groups the same relationship does not exist between the quantities of drug given and the concentrations obtained in the body fluids. For this reason, we undertook a study of the absorption and distribution of sulfapyrazine* in a group of infants and children with various infections, at the same time that we were attempting to determine the therapeutic value and the toxic effects of this drug.

Plan of Study. *Oral Administration.* Unselected hospitalized patients with various types of mild or moderately severe infections were given sulfapyrazine orally with as close adherence as possible to the following dosage scheme: 0.1 gm. per kilogram body weight was given as an initial dose, followed by 0.2 gm. per kilogram per 24 hours in 4 divided doses. Blood levels† of the free drug were determined at intervals during the course of several days of drug administration.

* We are indebted to Mead Johnson & Co., Evansville, Ind., through Dr. Warren M. Cox, Jr., of the Research Laboratory for the generous supply of sulfapyrazine and sodium sulfapyrazine used in this study.

† The sulfapyrazine determinations were carried out by the method of Bratton and Marshall[2] adapted to determination on 0.1 cc. of fluid. Because many of the patients were small infants, most of the blood samples were obtained by skin puncture. Therefore, in order to have comparable values, the determinations were made on whole blood except in certain isolated cases, although the level of drug in the plasma affords a better approximation of the level in the intercellular fluid.[5]

Subcutaneous Administration of Sodium Sulfapyrazine. Selected hospitalized patients with more severe infections were given sodium sulfapyrazine subcutaneously as a 0.5 or 1.0% solution in Ringer's or lactate-Ringer's solution. The dosage was varied as indicated in the charts, and frequent determinations of the levels of free sulfapyrazine in the blood and in some cases in the spinal fluid were made.

Therapeutic and Toxic Effects of Sulfapyrazine Administration. Careful observations of the clinical course and toxic effects were made on 236 cases with various types of infections treated at St. Louis Children's Hospital and 22 cases with meningococcus meningitis treated at the Isolation Hospital of St. Louis.
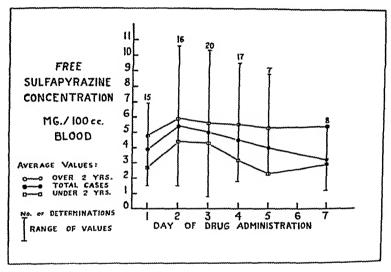
CHART 1.—Blood levels of free sulfapyrazine in patients receiving orally an initial dose of 0.1 gm. per kg. followed by 0.2 gm. per kg. per 24 hours in 4 divided doses.

Results. *Absorption of Sulfapyrazine Following Oral Administration.* Chart 1 shows the range and average blood levels of sulfapyrazine on successive days in a group of patients receiving the drug by mouth as indicated. The averages for the entire group and for those patients over and those under 2 years of age are shown separately. The average of all of the determinations for the entire group was 4.3 mg. per 100 cc.; for those over 2 years of age 5.3 mg. per 100 cc.; and for those under 2 years of age 3.3 mg. per 100 cc. Lower blood levels in infants on proportionate dosages have been noted with the other sulfonamide drugs.

In Chart 2 is shown the change in the free sulfapyrazine blood levels between the 4th and 6th hours after the oral administration of the drug in patients receiving the drug at 6 hour intervals. This change represents an average fall of only 11% which is similar to that observed with sulfapyridine and sulfadiazine and much less than that seen with sulfanilamide and sulfathiazole.

Blood Levels Following Subcutaneous Sodium Sulfapyrazine.   Chart 3 shows the blood levels of free sulfapyrazine observed over periods of from 5 to 12 hours in 5 patients who had each received a single subcutaneous injection of 10 cc. of a 1% solution of sodium sulfapyrazine per kilogram body weight.   Comparatively high blood levels were reached quite rapidly following the subcutaneous injection.   Chart 4 shows the *plasma* levels of free sulfapyrazine obtained on one patient who received the above dose on several different days.   Wide variations in the rate of urine flow on these different days were accomplished by forcing or restricting water by mouth preceding and during the experiments.*   Charts 5 and 6 show the blood levels of free sulfapyrazine obtained in different patients receiving repeated doses of sodium sulfapyrazine subcutaneously in the amounts indicated.   It may be
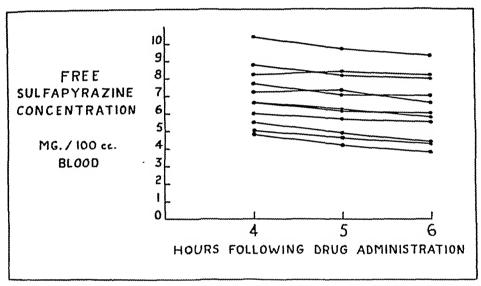
CHART 2.—Change in free sulfapyrazine levels between 4th and 6th hour in patients receiving drug orally in dosages approximately equivalent to 0.2 gm. per kg. per 24 hours at 6 hour intervals.

seen that after a high initial blood level of the drug has been attained by the subcutaneous administration of 40 cc. of 0.5% solution of sodium sulfapyrazine per kilogram body weight (see below), high concentrations can be maintained by repeated subcutaneous injections of 20 cc. of 0.5% solution of the drug per kilogram every 8 to 12 hours.   In some cases, however, there may be mounting drug concentrations in the blood, and in others there may be some falling off of the levels when the injections are repeated at these intervals.   In severely ill patients, it is desirable to obtain a high initial level of the drug in the body fluids as quickly as possible.   Chart 7 shows the rapidity with which this can be accomplished when 40 cc. of 0.5% solution of sodium sulfapyrazine per kilogram body weight is given.   Chart 8 shows the very

* From the plasma clearances determined on this patient,² it appears that these variations in plasma levels of sulfapyrazine following the subcutaneous administration of the sodium salt may be more directly related to variations in clearance than to variations in urine flow.

rapid rise in the blood concentration to levels of 30 to 40 mg. per 100 cc. within a few hours when 80 cc. of 0.5% solution is given in one injection or when 40 cc. is given and repeated after 2 to 5 hours. We
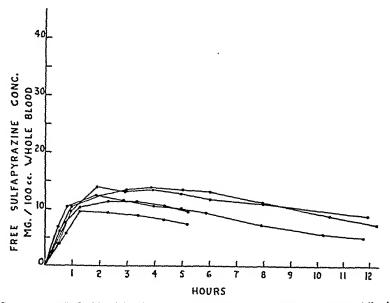
CHART 3.—Whole blood levels of free sulfapyrazine in different patients following single subcutaneous injections of 10 cc. of 1% solution of sodium sulfapyrazine per kg.
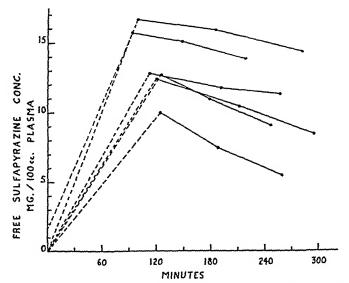
CHART 4.—Plasma levels of free sulfapyrazine in a single patient receiving subcutaneously 10 cc. of a 1% solution of sodium sulfapyrazine per kg. on each of several days.

believe that the subcutaneous administration of the sodium salt of sulfapyrazine offers several very definite advantages over the intravenous route of administration, particularly in infants and children. (See Discussion.)

Sulfapyrazine in Cerebrospinal Fluid.   Table 1 shows the relationship between plasma and spinal fluid concentrations of sulfapyrazine in patients with meningitis who were receiving repeated subcutaneous
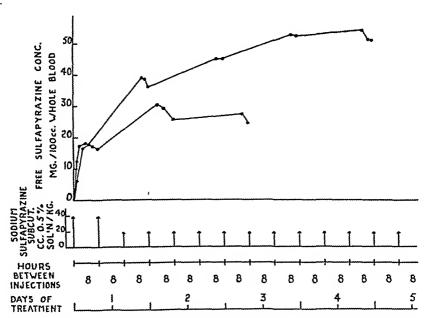
CHART 5.—Whole blood levels of free sulfapyrazine in 2 patients receiving subcutaneously repeated doses of 20 cc. of 0.5% solution of sodium sulfapyrazine per kg. every 8 hours after a high initial level had been established.
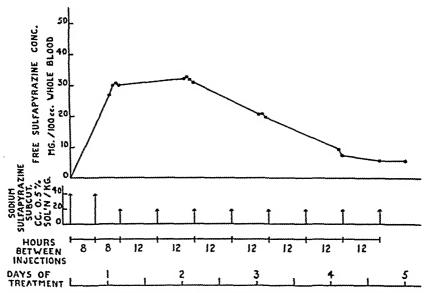
CHART 6.—Whole blood levels of free sulfapyrazine in 1 patient receiving subcutaneously repeated doses of 20 cc. of 0.5% solution of sodium sulfapyrazine per kg. every 12 hours after a high initial level had been established.

injections of sodium sulfapyrazine as shown in Charts 5 and 6.   Whole blood determinations were made at hourly intervals for periods of from 2 to 6 hours preceding the simultaneous sampling of plasma and spinal fluid, and during these periods the levels showed a maximum variation

of only 13.8%. We feel that a knowledge of the constancy of the blood levels preceding the simultaneous drawing of different body fluids for the purpose of studying distribution of substances is very important.[1] The per cent of the *plasma* concentration occurring in the spinal fluid varied from 50.8 to 81.8% with an average of 64.4% (76.2% of the whole blood level), which is somewhat higher than that observed by Hamburger and his associates,[5] who found 50 to 60% of the *whole blood* concentration in the spinal fluid 12 hours after the intravenous injection of sodium sulfapyrazine.
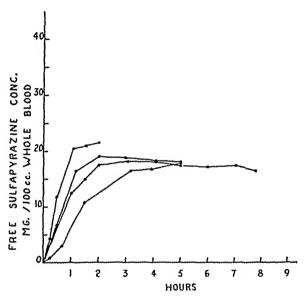
CHART 7.—Whole blood levels of free sulfapyrazine in different patients following single subcutaneous injections of 40 cc. of 0.5% solution of sodium sulfapyrazine per kg.

Evaluation of Therapeutic Effectiveness of Sulfapyrazine. In a period of 8 months between September 13, 1942 and May 14, 1943, 258 infants and children were treated with sulfapyrazine. No selection of cases was made, and the types of infections treated represented the wide variety commonly seen in a children's hospital. No single type of infection occurred frequently enough to allow a statistical comparison of the effectiveness of sulfapyrazine with that of other sulfonamide drugs previously studied.[6] However, patients with certain specific types of infections have served in the past as a basis for the evaluation of the effectiveness of other sulfonamide drugs,[6] and the results with sulfapyrazine in the treatment of these patients are reviewed.

Lobar Pneumonia. Only 18 cases of lobar pneumonia were treated. There were no deaths, and all showed the type of prompt *improvement* that has been observed with the use of sulfapyridine, sulfathiazole, and sulfadiazine.

Meningococcus Meningitis. Twenty-seven cases of meningococcus meningitis were treated. All of the patients recovered. Twenty-two of them were included in a larger series of cases of meningococcus

meningitis, to be reported by one of us (D.G.), in which approximately 200 patients in one epidemic were treated with either sulfapyridine, sulfadiazine, sulfathiazole, sulfamerazine, or sulfapyrazine. In this series no difference in the therapeutic effectiveness of the various drugs could be determined by clinical or laboratory means.

Erysipelas. Three cases of erysipelas or erysipeloid infection were treated with sulfapyrazine with the very prompt response expected from the use of other sulfonamide drugs.
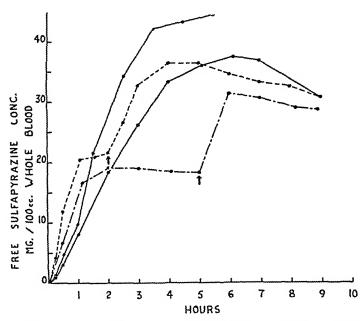
CHART 8.—Whole blood levels of free sulfapyrazine in different subjects following single subcutaneous injections of 80 cc. of 0.5% solution of sodium sulfapyrazine per kg. (————); and of 40 cc. per kg. repeated 2 hours (– – – –) and 5 hours (— - —) after first injection. Arrows indicate time of second injection.

Staphylococcus Infections. Eight cases of severe staphylococcus infection including 1 case of pneumonia; 5 cases of empyema, 1 with septicemia; and 2 cases of osteomyelitis with septicemia were treated with sulfapyrazine. The cases with septicemia received penicillin therapy also, and it was not possible in these or in the other cases to determine how much effect sulfapyrazine may have had on the course of the infection. It is thought, however, that there was no greater effect with sulfapyrazine than with other sulfonamide drugs.

Influenzal Meningitis. Five cases of influenzal meningitis were treated with sulfapyrazine. High concentrations of the drug in the blood and spinal fluid did not appreciably affect the course of the disease. All of these patients died. However, none of them was treated early in the course of the infection, and 4 of them were under 1 year of age. The 5th, a 2-year old child, had a chronic form of the disease.

Tuberculous Meningitis. Three cases of tuberculous meningitis were treated with very large amounts of the drug with no observable effect.

Bacillary Dysentery. Four cases of bacillary dysentery were treated. The response was good in each case.

Pyelitis. Four cases of pyelitis, in 3 of which the colon bacillus was recovered and in 1 of which no organism was found, were treated, and the improvement was very prompt.

Miscellaneous Infections. These included a large number of cases of non-specific upper and lower respiratory infections and several cases in which the drug was used prophylactically. An evaluation of the effectiveness of the drug in these patients is not possible.

Clinical Toxicity of Sulfapyrazine. Careful clinical observations and laboratory examinations relating to certain of the common toxic effects of other sulfonamide drugs were made on all the patients receiving sulfapyrazine.

Nausea and Vomiting. Nausea and vomiting clearly attributable only to sulfapyrazine did not occur in any case. This side-effect of the sulfonamide drugs occurs less frequently in infants and children than in adults, and in the former it is more difficult to determine whether the symptoms are due to the drug or to the infection for which the drug is being given. It seems clear, however, that sulfapyrazine causes as little or possibly less nausea and vomiting than the sulfonamide drugs commonly used at present.

Fever. Presumptive drug fever occurred in 5 cases. This number represents an incidence of only 1.9%.

Rash. No cases of cutaneous reactions due to sulfapyrazine were encountered. We do not feel that the failure to observe cutaneous reactions associated with sulfapyrazine administration to this number of patients indicates that such reactions will not occur. In our experience, however, it would be unusual with the other sulfonamide drugs, and particularly with sulfathiazole, for this number of cases to have been treated without the occurrence of drug rash.

Leukopenia. In no case was a leukopenia found which was thought to be due to sulfapyrazine. An analysis of the duration of drug treatment in all of the patients was not made, but many patients received the drug over a period of from 10 days to 2 weeks.

Acute Hemolytic Anemia. No cases of acute hemolytic anemia occurred in this series.

Renal Complications. Because of both their frequency and their seriousness, it is our feeling that the renal complications produced by the sulfonamide drugs, exclusive of sulfanilamide, constitute the most important of their toxic effects. Although there does not appear to be a strict correlation between blood levels of the drug or urinary output on the one hand and the occurrence of renal complications on the other,[1] the two factors mentioned do appear to bear some relation to the formation of renal calculi.[4] The lack of correlation, however, has suggested that other and unknown factors may be involved. For these reasons it is difficult to compare the incidence of renal complications from the various drugs as reported by different observers, and it is important that the height of the blood levels, particularly, be considered in relation to the occurrence of renal complications. In addition, it is

of greatest importance that the term renal complication be defined since some authors have limited it to the occurrence of pain over the kidneys, gross hematuria, and anuria or definite oliguria.[4]

In an analysis of the maximum blood levels of free sulfapyrazine observed, the cases were separated into two groups. The first includes 218 cases in which the blood levels of the free drug were less than 15 mg. per 100 cc. The second includes 40 cases in which the blood levels ranged from 15.3 to 59.4 mg. per 100 cc. (average 32.9 mg. per 100 cc.).

On the basis of clinical and laboratory findings, we have considered the cases of renal complications occurring in this series to be of two types. The first includes cases with only *transitory*, microscopic hematuria without any associated symptoms. These would have undoubtedly been overlooked had not careful, repeated examinations of the urine been made. This type occurred in 17 of the 218 cases in the first group, representing an incidence of 7.8%. There were 7 such cases in the second group of 40 patients, representing an incidence of 17.5%. In some of these cases it was difficult to be certain that there were more red cells in the urine than are commonly seen in the urine of severely ill infants and children not receiving a sulfonamide drug. The administration of sulfapyrazine was not discontinued because of this hematuria, and it subsided within a period of 1 to 3 days.

The second type of renal complication was that in which gross hematuria occurred. There were only 2 cases of this type in the entire series, representing an incidence of 0.78%. One of these cases occurred in each of the two groups described, representing an incidence of 0.46% in the group with lower blood levels and an incidence of 2.5% in the group with higher blood levels. In the former case there was no nitrogen retention or oliguria and the hematuria subsided in 1 day. In the latter case there was nitrogen retention and oliguria, both of which together with the hematuria gradually subsided over a period of 6 days after the drug was stopped.

It seems worth emphasizing that only one case of gross hematuria occurred in a group of 40 patients whose maximum blood levels of sulfapyrazine ranged from 15.3 to 59.4 mg. per 100 cc. (average level 32.9 mg. per 100 cc.*).

Other Toxic Effects. None of the other toxic effects which have been reported as due to other sulfonamide drugs was encountered in this series of cases treated with sulfapyrazine.

Discussion. Blood levels of free sulfapyrazine during oral administration of the drug in the dosages used are definitely lower than those obtained with equivalent dosages of sulfadiazine and possibly somewhat lower than those obtained with sulfathiazole. These lower blood levels occur particularly in patients under 2 years of age. They do not appear to be due to any greater difficulty in administering the drug

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* We did not make a special study of the effect of maintaining an alkaline urine on the incidence of renal complications. In the majority of the cases treated with sodium sulfapyrazine subcutaneously a lactate Ringer's solution was used in making the 0.5% solution of the drug.

by mouth. Low blood levels after oral administration of sulfapyrazine were also found by Hamburger et al.[5] in adult human subjects and by Schmidt and Sesler[8] in mice. These lower levels might seem to be a disadvantage in the treatment of infections in infants and children by the oral administration of sulfapyrazine, although Schmidt, Ruegsegger, Sesler, and Hamburger[9] have found in mice that the milligram for milligram antipneumococcal activity of sulfapyrazine is greater than that of sulfadiazine. Concentrations of free sulfapyrazine in the blood change so little from the 4th to 6th hour after the oral administration of the drug that quite uniform levels can be maintained by giving the drug at 6-hour intervals. Schmidt and Sesler believe that the superiority of sulfapyrazine over sulfanilamide, sulfapyridine, and sulfathiazole in the treatment of beta hemolytic streptococcus infections in mice is due largely to the maintenance of effective concentrations in the blood during the entire period between administrations. In mice they found also that increasing the oral dosage of sulfapyrazine produced smaller increases in the concentration in the blood than were produced by the other sulfonamide drugs. Although we did not investigate this point specifically, the low blood levels observed in a few patients receiving very large dosages of sulfapyrazine by mouth suggest that it is also true for human patients. Schmidt and Sesler attribute this finding to the slow absorption of the drug from the gastrointestinal tract. The fact that high blood levels are maintained with comparable amounts of the drug given parenterally (see below) indicates that the low levels after oral administration are not due to rapid excretion.

TABLE 1.—RELATIONSHIP BETWEEN WHOLE BLOOD, PLASMA AND SPINAL FLUID CONCENTRATIONS OF FREE SULFAPYRAZINE IN 3 PATIENTS WITH MENINGITIS TREATED WITH SODIUM SULFAPYRAZINE SUBCUTANEOUSLY

Case	Day of drug administration	Variation in whole blood levels of sulfapyrazine preceding plasma and spinal fluid sampling		Free sulfapyrazine concentration mg./100 cc.			Whole blood concentration of sulfapyrazine present in spinal fluid (%)	Plasma concentration of sulfapyrazine present in spinal fluid (%)
		%	Hours	Whole blood	Plasma	Spinal fluid		
M. A.	1	11.0	6	16 4	20.7	10.5	64 0	50 8
	2	5 7	7	25.7	32 5	22 9	89 1	70 6
	3	11 2	2	24 6	28 6	23 4	95 1	81 8
J. P.	2	3.7	3	36 2	44 1	29 5	81 5	67 0
	4	0.7	3	53 0	58 9	40 6	76 6	69 0
	5	2.9	3	52 1	59 5	39 2	75 2	65 8
S. S.	2	13 8	3	30 2	36 0	18 6	61.9	51 7
	3	5.6	3	31 2	35 2	20 6	66 0	58 6
					Average		76 2	64 4

When high concentrations of the drug in the blood are desired, they can readily be attained by the parenteral administration of the sodium salt. We have limited our investigations to the subcutaneous administration of sodium sulfapyrazine because we feel that, at least in infants and children, its advantages are great enough to warrant its entirely replacing intravenous administration. By giving a 0.5% solution of

the sodium salt subcutaneously, the difficulties of intravenous administration in small infants are avoided. Very high blood levels can be attained within a period of 1 to 3 hours after beginning the administration, and at the same time the volume of fluid in which the drug is dissolved assures a good fluid intake. If very high levels are to be attained by intravenous administration to a patient with severe dehydration, lost fluids should first be replaced. With subcutaneous injection, however, this replacement of fluid is accomplished as the drug is being given, and consequently high blood levels may be attained just as rapidly. A final advantage of the subcutaneous over the intravenous route of administration is that the high blood concentrations are reached by a rapid rise *to* that level avoiding the excessively high levels which follow immediately after intravenous injections and during which the dangers of renal complications may be increased.

The percent of the plasma concentration of sulfapyrazine occurring in the spinal fluid (64%) is similar to that observed with sulfapyridine and sulfadiazine.

Our data do not allow any statistical comparison between sulfapyrazine and the other sulfonamide drugs as to effectiveness against the various infections in infants and children. However, a sufficient number of patients were treated and studied to warrant the opinion that with the dosages of sulfapyrazine and sodium sulfapyrazine employed, the effectiveness equals that of the other sulfonamide drugs.

It has been our feeling that a sulfonamide drug as effective as the ones now commonly used but one which produces fewer renal complications would be most desirable. It appears from our series that sulfapyrazine produces fewer severe renal complications than the sulfonamide drugs now commonly used with the exception of sulfanilamide. This seems particularly to be true in cases in which high blood levels of the drugs are maintained over a period of days.

Other toxic effects attributable to the sulfonamide drugs occurred no more and possibly less frequently in this series of patients treated with sulfapyrazine than would have been expected in series similarly treated with any other of the sulfonamide drugs.

Summary. From a study of the use of sulfapyrazine and sodium sulfapyrazine in the treatment of infections in a group of 258 infants and children, it was found that:

1. Comparatively low blood levels of free sulfapyrazine follow the oral administration of the usual amounts of the drug.

2. Comparatively uniform blood levels are maintained when the drug is given by mouth at 6-hour intervals.

3. High blood levels of the drug can be rapidly attained and maintained by the subcutaneous administration of sodium sulfapyrazine.

4. An average of 64.4% of the amount of sulfapyrazine in the plasma (76.2% of that in the whole blood) was found in the spinal fluid.

5. With comparable blood levels, the therapeutic effectiveness of sulfapyrazine appears to be equal to that of any of the commonly used sulfonamide drugs.

6. Sulfapyrazine appears to cause few toxic effects, and the renal complications appear to occur less frequently with the use of this drug than with other sulfonamide drugs except sulfanilamide.

REFERENCES

1. Barnett, H. L.: J. Pediat. (in press).
2. Barnett, H. L., and Perley, A. M.: To be published.
3. Bratton, A. C., and Marshall, E. K., Jr.: J. Biol. Chem., 128, 537, 1939.
4. Dowling, H. F., and Lepper, M. H.: J. Am. Med. Assn., 121, 1190, 1943.
5. Hamburger, M., Jr., Ruegsegger, J. M., Brookens, N. L., and Eakin, E.: Am. J. Med. Sci., 204, 186, 1942.
6. Hartmann, A. F., Barnett, H. L., Perley, A. M., and Ruhoff, M. B.: J. Missouri Med. Assn., 37, 41, 1940.
7. Heinemann, M.: J. Clin. Invest., 22, 29, 1943.
8. Schmidt, L. H., and Sesler, C. L.: J. Pharm. and Exp. Ther., 77, 277, 1943.
9. Schmidt, L. H., Ruegsegger, J. M., Sesler, C. L., and Hamburger, M., Jr.: J. Pharm. and Exp. Ther., 73, 468, 1941.

STUDIES ON THE PENETRATION OF SULFONAMIDES INTO THE SKIN

II. Sulfathiazole, Sulfadiazine and Sodium Sulfacetimide*

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In the first report of this series,[11] a method was described for studying the rate and degree of absorption of sulfonamides into the intact skin of guinea pigs and humans from various ointment bases. Whereas most workers estimate topical absorption by blood levels, this paper described sulfonamide analyses of skin biopsies. The time of application of the ointment, and the concentration of sulfanilamide in the various ointment bases were varied.

It was concluded that there was no correlation between the degree of penetration of sulfanilamide and the type of ointment base, at least in regard to whether the base is of the water-in-oil or the oil-in-water type. Concentration of sulfanilamide has little effect on tissue levels reached, but time of application had some effect.

In the present report, 3 additional commonly used sulfonamides have been studied, with the same objectives, namely to determine the effect of concentration, time of application, and type of ointment base. In addition, a few studies are included in which, instead of intact skin,

absorption by injured skin is described.   Moreover, studies were made on absorption from wet-packs of sulfonamide solutions, the effects of detergents and solubilizers, and finally the relative retention of sulfonamides by the skin after topical application.

Methods.   The methods of applying the sulfonamides to the skin of guinea pigs held in confining cages, and the method of analysis of skin biopsies after different application times, was described in detail in the first paper of this series.[11]   It is necessary only to repeat here that the excess sulfanilamide and ointment were washed off the skin with soap and warm water, followed by shaving and rinsing with warm water; that the biopsies weighed approximately 100 mg.; and that the biopsies were hydrolyzed in hot HCl prior to coupling, diazotizing, and determining total sulfonamides in the filtrates by a photoelectric method.

The same 7 different ointment bases that were studied in the first report[11] were used, 2 oil-in-water emulsion type bases (O/W), and 5 water-in-oil (W/O). The emulsion types were determined microscopically on samples stained with Sudan III, and by the conductimetric method.*   The compositions were as follows:

<div align="center">

OINTMENT BASES

Oil-in-water   %

</div>

1.†Sodium lauryl sulfate	1
Stearyl alcohol	11
Cetyl alcohol	3
Spermaceti	11
Glycerin	11
Water	63
2.‡Liquid petrolatum	41
Peanut oil	2
Triethanolamine	1
Stearic acid	3
Cetyl alcohol	2
Water	51

<div align="center">

Water-in-oil   %

</div>

1. Petrolatum	60
Stearyl alcohol	20
Water	20
2.§A base consisting of oleic acid, white petrolatum and oleic acid esters and amides of diethanolamine	
3. Petrolatum	50
Lanolin (anhyd.)	50
4.×A base consisting of alcohols, and cholesterol esters in petrolatum	
5. Cod-liver oil	20
Lanolin (anhyd.)	20
Petrolatum	55
Paraffin	5

The sulfonamides were incorporated in these bases at concentrations of 1, 5, 10 and 20%, by tile and spatula.

* Base 1 was classified by error as O/W base C in the first paper.[11]
† Modified from Pillsbury *et al.*[8]
‡ Modified from Hawking.[4]
§ Hydrosorb (Abbott).
× "Aquaphor" (Duke).

Experimental.   1. *Sulfathiazole Ointments.*   Five and 10% concentrations of sulfathiazole in the 7 bases, and 1, 5, and 10% concentrations in Base 2, were compared, with application times of 1 and 3 days (2 applications daily).   The results are summarized in Table 1, including a few human cases.   The data is given as mg. per 100 cc. total sulfonamide concentration per 100 gm. wet weight of skin.   Each figure represents averages of at least triplicate determinations from 1 piece of skin, that is 3 skin aliquots per biopsy.   Each experiment was repeated at least 4 times.   In many cases more than 3 aliquots were taken from each piece of skin.

TABLE 1.—PENETRATION OF SULFATHIAZOLE (SAT) INTO THE INTACT SKIN OF GUINEA PIGS AND HUMANS FROM VARIOUS OINTMENTS

Type of emulsion	Ointment base	1% SAT ointment. Av. mg. SAT per 100 gm. skin, after		5% SAT ointment. Av. mg. SAT per 100 gm. skin, after		10% SAT ointment Av. mg. SAT per 100 gm. skin, after	
		1 day	3 days	1 day	3 days	1 day	3 days
W/O	1	..	..	2.8	3 6	3 1	3 8
	2	5.6	7.5	4 6	6.4	4 1	7.9
		*5 1**	*7 3*	*6 6*	*7.8*	*5 6*	*5 8*
	3	..	..	2 5	3.2	2 8	4 2
	4	..	..	4 3	4.3	2 7	4 7
	5	..	..	2 5	3 2	2 7	3 7
O/W	A	..	..	3 0	3.2	3 1	3 8
	B	..	..	4 7	6 8	4 0	5 3

* Italics are human analyses.

It is seen that concentration of sulfathiazole has no effect on skin absorption, and that the time of application has a slight effect.   The frequency of application may have an effect, but since 1 to 2 applications were made daily, this is doubtful.   It is also seen that the type of ointment base used has little or no effect, at least with respect to the type of emulsion, whether of the oil-in-water, or the water-in-oil.

2. *Sulfadiazine Ointments.*   Since there was no appreciable concentration effect, but a slight time effect with sulfanilamide[11] and sulfathiazole, it was decided to study the time and concentration effect of sulfadiazine at 1 and 10% concentrations only in one base.   In this case, Base 2 was selected since it has been studied more extensively than the other bases, and comparisons could thus be made with the other sulfonamides.   To determine the effect of the various bases, *1% sulfa*diazine in the 7 bases was studied, and the biopsy concentrations were determined after 3 days application time.   Table 2 shows the results.

Concentration has little effect except at 1 day application time, and time had a small but definite effect.   Base 2 gave the best penetration, but there was no effect of the type of emulsion base, as in the case of sulfanilamide and sulfathiazole.

3. *Sodium Sulfacetimide.†*   This salt was included in this study because of its high solubility and relatively low pH in comparison to the sodium salts of sulfathiazole, sulfadiazine, and sulfapyridine. The solubility of sodium sulfacetimide in water at room temperature

is 56.9%, with a pH of 9.5. At a 20% concentration in plasma, the pH is 7.68.[9] The sodium salts of the other sulfonamides, because of their high alkalinity, have been avoided in topical application, although Fox[1] claimed that sodium sulfadiazine is tolerated in fairly high concentrations, in contrast to sodium sulfathiazole.

TABLE 2.—PENETRATION OF SULFADIAZINE (SAD) INTO THE INTACT SKIN OF GUINEA PIGS FROM VARIOUS OINTMENTS

Type of emulsion	Ointment base	1% SAD ointment. Av. mg. SAD per 100 gm. skin, after		10% SAD ointment. Av. mg. SAD per 100 gm. skin, after	
		1 day	3 days	1 day	3 days
W/O	1	..	3.1		
	2	3.6	6.3	5.1	6.6
	3	..	2.9		
	4	..	3.6		
	5	..	3.9		
O/W	A	..	3.0		
	B	..	3.6		

In this study, 1, 10 and 20% sodium sulfacetimide in Base 2 were compared. The salt was first dissolved in a minimal volume of water and the resulting solution was emulsified with the melted base, using an egg beater. The effect of the various bases was studied, using only a 1% concentration, as in the case of sulfadiazine.

Table 3 shows the results.

TABLE 3.—PENETRATION OF SODIUM SULFACETIMIDE (NaSAC) ("ALBUCID SOLUBLE") INTO THE INTACT SKIN OF GUINEA PIGS AND HUMANS FROM VARIOUS OINTMENTS

Type of emulsion	Ointment base	1% NaSAC ointment. Av. mg. NaSAC per 100 gm. skin, after		10% NaSAC ointment. Av. mg. NaSAC per 100 gm. skin, after		20% NaSAC ointment. Av. mg. NaSAC per 100 gm. skin, after	
		1 day	3 days	1 day	3 days	1 day	3 days
W/O	1	3 3	7.3				
	2	5.5±1.6	12.4±3.6	6 0±2.2	14 2±3 6	5 1±1 8	21 3±2 8
		5 8	*14 7*	*6 9*	*19 2*		
	3	2 2	6.0				
	4	3.0	4 2				
	5	2 0	4.6				
O/W	A	3.5	4.6				
	B	5.2	5 0				

* Italics are human analyses.

Concentration has some effect, and time had a marked effect. The levels reached were higher than those with the less soluble sulfonamides already described. Base 2 gave a higher absorption than the other bases, but the emulsion type base had no effect, as with the other sulfonamides studied.

The sodium salts of sulfathiazole, sulfadiazine, and sulfapyridine caused saponification of some of the bases, and skin maceration, and were not studied.

4. *Solubilizers and Detergents.* It seemed plausible since sulfanilamide, sulfathiazole and sulfadiazine are little soluble in water, that the use of better solvents such as propylene glycol[14] and detergents and

solubilizers such as aerosol, to ointment bases, might increase the absorption of the sulfonamides.

Studies were therefore carried out with 1 and 10% sulfathiazole in a base consisting of propylene glycol 10%, aerosol (OT–70) 0.5%, Base 2 q.s. 100%. The sulfathiazole was suspended in the warm glycol, aerosol mixture, and then emulsified with the melted base with a beater. Skin concentrations after 1 and 3 days application time were almost identical with those obtained with the corresponding concentrations of sulfathiazole in Base 2 without the glycol and aerosol. It is difficult to incorporate higher concentrations of propylene glycol into ointment bases, as separation occurs, and although this probably could or has been done, higher concentrations probably would not cause higher penetration in intact skin. Injured skin might be entirely different, but we have not studied this problem. Herrmann *et al.*[6] developed new vehicles containing aerosol, xylene, antipyrene, and propylene glycol, which may have definite advantages as bases for sulfonamides. These workers also mention that they have developed histochemical methods for investigating sulfonamide penetration into skin. Such an approach would be of great interest if they could reveal the pathways of absorption.

5. Studies on Injured Skin. The hair on the left side of anesthetized guinea pigs was closely clipped and the skin injured with coarse sandpaper, rubbing until bleeding occurred. The uninjured skin on the right side of the same animal served as a control.

The studies were carried out with 1 and 10% concentrations of sulfanilamide and sodium sulfacetimide in Base 2. Tissue biopsies and analyses were made after 2 and 6 hours application time. The ointment was reapplied several times during this period.

In order to compare the penetration from an ointment with that from wet packs as two different methods of topical applications, a few data are included to illustrate this, although the present report does not purport to examine in detail the absorption from wet packs and solid powder. The penetration from Base 2 was compared with the penetration of 1% sulfanilamide from a wet pack consisting of several layers of gauze which was kept saturated with a 1% aqueous solution containing 0.1% aerosol. This detergent was used to cause wetting at hair bases and of the oily skin. Uniform results were not obtained without its use presumably because of lack of uniform wetting caused by the presence of the hair which occluded air bubbles. A similar comparison was made between 10% sodium sulfacetimide in Base 2, *versus* 10% aqueous solution containing 0.1% aerosol. The results are seen in Table 4.

As expected, removing the barrier of the intact skin increases the absorption of both sulfonamides, and levels were reached within the short period of 6 hours which far exceeded those found after 3 days application time to intact skin. Moreover, concentration of sulfonamide had a marked effect on skin absorption in contrast to intact skin. This indicates that in practical use, concentration would be an impor-

tant factor where injured areas are treated, but not for relatively unbroken, cornified or scarified areas.

TABLE 4.—PENETRATION OF SULFANILAMIDE (SNA) AND SODIUM SULFACETIMIDE (NaSAC) INTO THE INTACT AND INJURED SKIN OF GUINEA PIGS FROM AN OINTMENT AND FROM WET PACKS

		1% SNA Av. mg. SNA per 100 gm. skin, after		10% SNA Av. mg. SNA per 100 gm. skin, after	
Vehicle		2 hrs.	6 hrs.	2 hrs.	6 hrs.
Ointment base 2	Normal skin	1.2	1.6	1.9	3.6
	Injured skin	4.1	5.2	10.9	25.8
Water + 0.1% aerosol	Normal skin	1.8	2.8		
	Injured skin	30.4	28.9		
		1% NaSAC		10% NaSAC	
Ointment base 2	Normal skin	1.5	3.2	2.0	4.5
	Injured skin	5.2	7.1	26.4	41.0
Water + 0.1% aerosol	Normal skin	..	..	3.2	7.4
	Injured skin	..	..	252.0	288.0
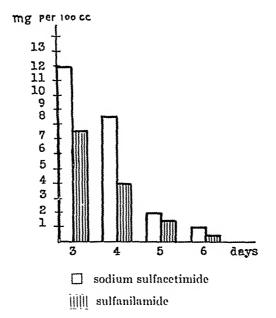
FIG. 1.—Retention of sulfonamides by guinea pig skin. One per cent sodium sulfacetimide (NaSAC) and 1% sulfanilamide (SNA) in ointment base 2 applied for 3 days, then removed. Ordinates show mg. total sulfonamide per 100 gm. skin after 3, 4 and 5 days from the time of the first applications.

6. *Skin Sulfonamide Retention.* One per cent sodium sulfacetimide and sulfanilamide in Base 2 were applied twice daily for 3 days, after which time the skin was washed as previously described. Biopsies were performed after 3, 4 and 5 days from the time of the first application, in order to determine the degree of skin retention of sulfonamide after the external reservoir was removed. The results are seen in Figure 1. Each histogram represents the average of 3 animals per experiment and 15 tissue determinations per point.

It is seen that the skin concentrations drop to therapeutically negligible levels after the 5th day, in both cases, even though the

original sodium sulfacetimide level was higher than the sulfanilamide level. No studies of this nature were deemed necessary in injured skin, as retention would be very small. Hawking[5] has made such studies, using different methods. Goodwin and Findlay[3] have also studied absorption of locally applied sulfonamides by experimental wounds.

Discussion. Several workers have investigated the diffusion of various sulfonamide mixtures out of certain bases, such as emulsions, resins, jellies, pastes, creams and the like, into agar and into flowing water (Waud and Ramsay,[13] Fuller et al.,[2] Strakosch and Olson[12] and others). The results of these studies are more applicable to the diffusion of sulfonamides into open wounds than into intact skin, as has been borne out by the work of Fuller et al.,[2] who has studied the absorption and retention of sulfonamides in experimental wounds. But such studies are not as applicable to a study of penetration into normal intact skin, and probably so even in injured skin, since the skin barrier cannot be regarded as a sample aqueous or lipid phase.

For this reason we believed that the only logical approach to the problem of skin penetration by sulfonamides was by direct in vivo experiments, analyzing skin biopsies for total sulfonamide.

Many workers have used either water-in-oil or oil-in-water emulsion bases for incorporation of certain sulfonamides to be used in skin conditions, usually recommending on theoretical grounds only, oil-in-water bases. The present studies show no effect of the type of base, under the experimental conditions described. The increased interest in the topical application of the sulfonamides, especially in ointment form, is manifested in the numerous preparations which have been advocated. Since various workers have recommended not only different sulfonamides in different bases, but also various concentrations of drugs to be incorporated, the resulting confusion has been great. The literature on sulfonamide ointments is too extensive to be reviewed at this time, although reference may be made to Spink's new edition on sulfonamides,[10] in which topical and dermatologic uses of sulfonamides are discussed, and in Kalz and Prinz' paper[7] in which the literature is reviewed.

The lack of effect of concentration of sulfanilamide,[11] and of sulfadiazine and sulfathiazole on penetration into intact skin suggests that an unnecessary expense may have been associated with the use of higher concentrations in cases in which the skin barrier is relatively intact.

The lack of effect of the type of emulsion base suggests, in confirmation of some of Fuller's et al. results,[2] that caution be exerted in extending theoretical deductions or in vitro data, to in vivo conditions.

Sodium sulfacetimide gave the best penetration into intact skin, suggesting further consideration of this sulfonamide, which is widely used in England, under the trade name of "Albucid soluble" (Schering), even at concentrations of 5% topically applied to the eye.

The fact that removal of the epithelial barrier by injury increased the effect of sulfonamide concentration on absorption by the skin, sug-

gests that higher concentrations be used in cases in which skin lesions have more extensively removed the skin barrier. Hawking[3] and Fuller et al.[2] have recommended the use of microcrystalline sulfathiazole or sulfadiazine in cases in which a more protracted absorption is desired and where wet packs are not called for, and the use of water-in-oil bases for ointment application where more protracted absorption is desired.

Summary. 1. *In vivo* experiments on guinea pigs and humans have been performed, to determine the penetration of sulfonamides from various vehicles, into the skin. Skin biopsies were analyzed for total sulfonamide concentration after varying times of applications.

2. Sulfanilamide,[11] sulfathiazole and sulfadiazine, in a comparable base at comparable concentrations and times of application, gave comparable tissue levels, demonstrating no difference in penetration into intact skin. Sodium sulfacetimide ("Albucid soluble"), on the other hand, gave greater penetration after a 3 day application time, than the sulfonamide bases tested.

3. Increasing the concentration of sulfonamide in comparable ointment bases did not increase the absorption by the intact skin of sulfanilamide,[11] sulfathiazole and sulfadiazine. Even sodium sulfacetimide showed only a slight effect of concentration.

4. Increasing the time of application increased the skin absorption of sulfonamide in all cases, especially of sodium sulfacetimide.

5. Of 7 ointment bases examined, 2 oil-in-water and 5 water-in-oil emulsions, the type of emulsion had no effect on the absorption of sulfonamide by the skin, including the sodium sulfacetimide. One water-in-oil emulsion, Base 2, was superior to the others tested.

6. An ointment containing a solubilizer and a wetting agent in greater amounts than in the other bases studied, did not give better absorption of sulfathiazole by the skin than the other bases.

7. Injured skin absorbs much greater amounts of sulfonamides from ointments than intact skin. Sodium sulfacetimide is especially penetrating into injured skin.

8. Injured skin absorbs sulfonamides from wet packs to a much greater extent than from ointments.

9. Some experiments on the retention of sulfonamides by the skin after termination of application, are reported. Negligible levels are encountered after 5 days.

REFERENCES

1. Fox, C. L., Jr.: Arch. Surg., 45, 754, 1942.
2. Fuller, A. T., Hawking, F., and Partridge, M. W.: Quart. J. Pharm. and Pharmacol., 15, 136, 1942.
3. Goodwin, L. G., and Findlay, G. M.: Lancet, p. 691, May 31, 1941.
4. Hawking, F.: Lancet, p. 507, Oct. 31, 1942.
5. Hawking, F.: Lancet, p. 786, June 21, 1941.
6. Herrmann, F., Sulzberger, M. B., and Baer, R. L.: Science, 96, 451, 1942.
7. Kalz, F., and Prinz, M. V. H.: Canad. Med. Assn. J., 46, 457, 1942.
8. Pillsbury, D. M., Wammock, V. S., Livingood, C. S., and Nichols, A. C.: Am. J. Med. Sci., 202, 808, 1941.
9. Schering Corporation: Bloomfield, N. J., personal communication.
10. Spink, W. W.: Sulfonamides and Related Compounds in General Practice, 2d ed., Year Book Publ., 1942.

11. STRAKOSCH, E. A., and CLARK, W. G.: Am. J. Med. Sci., 205, 518, 1943.
12. STRAKOSCH, E. A., and OLSON, V. M.: Arch. Dermat. and Syph., 46, 44, 1942.
13. WAUD, R. A., and RAMSAY, A.: Canad. Med. Assn. J., 48, 121, 1943.
14. YONKMANN, F. F., LEHMAN, A. J., and CHASE, H. F.: Fed. Prod. Am. Soc. Exp. Biol., 1, 172, 1942.

GASTROPHOTOGRAPHY IN NATURAL COLORS IN CONJUNCTION WITH GASTROSCOPY*

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SOME gastrophotographic studies in natural colors, which were made in conjunction with gastroscopy, have been published in a preliminary report.[2] This investigation has been continued further in a series of patients who presented diagnostic and therapeutic problems.

Clinical Study. Altogether 41 patients were studied: 27 males and 14 females. Their ages ranged from 21 to 77 years. The gastroscopic findings in these patients were as follows: a gastric ulcer in 9 patients; carcinoma of the stomach in 14; hypertrophic gastritis in 8; chronic gastritis, in which the superficial type predominated, in 4; deposits of barium sulfate particles adherent to the mucous membrane of the stomach in 1 patient (E. S. whose case report will be described); no gastric lesions in 5 patients. The latter were studied because 2 of the patients had Roentgen ray evidence of duodenal ulcer with pyloric obstruction; another patient, C. W., who had a gastro-enterostomy performed 25 years ago, was admitted for a gastric hemorrhage; 1 patient, W. H., had a questionable Roentgen ray diagnosis of a gastric ulcer; the 5th patient, M. R., had Roentgen ray evidence of a prepyloric ulcer (this case report will also be described).

Method of Procedure. The method of procedure was as follows: After the patient had been gastroscoped with the Wolff Schindler flexible gastroscope, the gastric area which was the site of interest was noted. The distance from the incisor teeth to the depth to which the gastroscope had been introduced was outlined on the flexible tube to which the Gastro-Photor camera was attached. The latter was then inserted to this depth. The photographs, which were taken on Kodachrome film, were developed and enlarged. The endoscopic and photographic studies, in natural colors, were compared with the operative findings as well as the subsequent clinical course.

Of the 41 patients who were observed, the gastrophotographic studies in 26 (63.4%) corresponded to the endoscopic findings. The gastrophotographic studies revealed the following: a gastric ulcer in 5 patients; carcinoma of the stomach in 8; hypertrophic gastritis in 5; chronic gastritis, in which the superficial type predominated, in 2; barium sulfate particles adherent to the mucous membrane of the stomach in 1; no gastric lesion seen in 5 patients. In 15 (36.6%) of the cases the gastrophotographs did not record the endoscopic findings. Four of these patients were suffering from a gastric ulcer; 6 from car-

FIG. 1. K. W. A benign prepyloric ulcer.

FIG. 2.—K. W. Another view of the benign prepyloric ulcer.

FIG. 3.—M. R. Gastrophotograph of gastroscopic view, which appears to be the pyloric outlet, but which actually is beyond the field of visualization. The opening seen in the photograph represents the end of a canal in which there was a carcinoma.

cinoma of the stomach; 3 from hypertrophic gastritis, and 2 from chronic gastritis in which the superficial type predominated.

As was illustrated in the preliminary report,[2] the normal mucous membrane and malignant lesions of the stomach were definitely outlined. They were also clearly seen in the gastrophotographs in this study. Six of the 8 patients with carcinoma of the stomach came to operation. In 4 of these the lesion in the resected part of the stomach had the same color and appearance which were observed in the endoscopic examination and in the gastrophotographs. In 2 of the patients who were operated upon, the lesion appeared to be grayish white in the resected specimen, while in the gastroscopic and gastrophotographic studies, the carcinoma seemed to be definitely greenish in color. This difference in color can be explained on the basis that there was a regurgitation of bile during the endoscopic and photographic examinations. In one case the gastroscopy revealed that the carcinoma was arising from one point and that the rest of the mucous membrane was intact. This was corroborated by the gastrophotographs, and was further verified at operation. Atrophy of the mucous membrane which was seen in cases of malignancy could be readily identified in the gastrophotographs. In one case the latter showed nodules of a carcinomatous lesion in a part of the stomach which was not seen endoscopically.

In the preliminary report[2] it was stated that benign ulcers of the stomach did not photograph very well. This difficulty has been materially overcome as can be seen in Figures 1 and 2. This was a gastrophotograph of K. W., a 39 year old white woman who had a prepyloric ulcer on the lesser curvature. The patient was treated by means of duodenal alimentation. Three weeks later the patient was again gastroscoped, and at this time the ulcer had healed to such an extent that it was hardly visible. There was not enough of it present to be photographed.

During this study, areas were observed presenting the cobblestone appearance or raised beading of the rugal folds which have been described as typical for hypertrophic gastritis. These fields were clearly seen in the gastrophotographs just as they were observed gastroscopically. Areas of hypertrophic gastritis were seen in cases with and without peptic ulcer. In one case the camera caught the edge of the prepyloric ulcer, with the hypertrophic gastritis contiguous to it and enlarged folds in the rest of the stomach with a normal mucosal pattern.

In one of the photographs, the edge of a bleeding ulcer of the stomach was seen. In addition, raised enlarged folds could be clearly outlined. These rugal folds did not present the appearance of an atrophic or a hypertrophic gastritis. While the folds appeared raised, the mucous membrane was dull and swollen, giving a widespread appearance to it. Gastroscopically the impression was that of hyperplasia and not atrophy or hypertrophy, and hence these areas were termed "hyperplastic gastritis." Maher and her co-workers[1] regarded the presence of hyperplasia (increase in the number of glands and in the size of the gland cells) as essential in the microscopic diagnosis of hypertrophic

gastritis. The endoscopic view of the hyperplastic areas which I observed did not correspond, macroscopically, to that described as hypertrophic gastritis, and as outlined before,[3] it may be misleading to designate them as such. These hyperplastic areas have been seen gastroscopically in benign and malignant lesions of the stomach and in 2 cases of ileitis. In the latter there was definite endoscopic evidence of improvement in the stomach when the inflammatory process in the small intestines subsided. Gastroscopically it is not always possible to differentiate between the hyperplastic areas and possible malignant affections of the stomach.

The combined gastroscopic and gastrophotographic examinations were very helpful in the differential diagnosis between benign and malignant lesions of the stomach. In the photograph the sharp line of demarcation of the benign lesion was clearly outlined as can be seen in Figures 1 and 2. The base of the ulcer appeared as a dark blank space. The contiguous areas around it did not have the atrophic appearance to the mucous membrane which was seen in carcinoma. In the latter there was no sharp line of demarcation and the base of the lesion was irregular in appearance and presented the various colors seen gastroscopically. Furthermore, these lesions as a rule gave the impression that they started "nowhere and ended nowhere."

In this study gastrophotography served another purpose, namely, as a check on the clinical appraisal of gastroscopy both from the standpoint of the procedure and the gastroscopist. The latter may see a certain area and interpret his impression accordingly. If the operative findings do not tally with the endoscopic interpretation, the question arises as to whether the gastroscopist saw the involved area. When, however, a photographic record is made of the gastroscopic findings then there can be no doubt as to whether the involved area was seen. The following case will illustrate this point:

Case Study. M. R., 64 years old, stated that for 10 years she had had periodic attacks of upper right quadrant pain which was diagnosed as biliary colic. Gall stones were demonstrated by cholecystography. She said that for the past 6 months she had felt pain in the epigastrium, which would come on about 1 to 2 hours after meals, was located across the stomach, did not radiate and was relieved by food. Nausea occurred frequently. The patient had lost 10 pounds about 6 months ago, but she had regained 4 pounds the past month. After Roentgen radiation at another institution she was told she had a gastric ulcer. This was corroborated by another roentgenologist who reviewed the films. Gastric analysis revealed HCl 50, acidity 60, blood negative. The stools were negative for blood. The gastroscopic examination revealed what appeared to be a normal pyloric outlet. Gastrophotography corroborated these findings (Fig. 3). The patient was operated upon. Cholelithiasis was found. The surgeon also felt what he thought was an ulcer crater at the pylorus. A resection of the pyloric end of the stomach was performed, which was reported by the pathologist as carcinoma of the stomach (linitis plastica). What was seen gastroscopically proved to be one end of a cicatrized canal in which there was a small carcinoma, starting 0.5 mm. from the pyloric end which was 2.5 mm. wide. The pyloric outlet was beyond the field of visualization, although as stated before, endoscopically and photographically, it appeared that the pyloric outlet was visualized.

Comment. The criticisms leveled against previous attempts to photograph the gastric wall included blind photography, questionable interpretation of the films, and, where the rigid gastroscope was used, the risk involved. Therefore, the combined examinations, using the flexible gastroscope in conjunction with the Gastro-Photor camera and taking the films in natural colors represents an advance in this field.

Of the 41 cases observed in this study, the gastrophotographs corresponded to the endoscopic findings in 26 (63.4%) of the cases. In 15 (36.6%) of the cases the lesion, which was seen gastroscopically, was not recorded in the photographs. In 11 of the 15 patients, the gastrophotographs were more or less blurred or they showed whitish circular areas, characteristic of deposits of mucus. In some of these photographs, parts of the gastric wall were indistinctly visualized. These photographic results can be explained on the following basis: At times during the gastroscopy, especially in the nervous individuals or when the endoscopic examination was prolonged, an excessive amount of secretion accumulated. The hypersecretion, while it did not interfere with a satisfactory gastroscopic view of the lesion, was sufficient to prevent a photographic record of it. If the camera dipped into a mucous lake, the gastrophotographs were partially or completely blurred. Even if the camera did not strike one of these areas, but if the lesion was sufficiently covered with mucus, the whitish circular areas, mentioned above, were recorded but the lesion was not seen. In 4 of the 15 patients, the gastric wall was clearly outlined but the lesion was not visualized. In 2 of these patients, the subjects changed their position just as the photographs were being taken, thereby probably shifting the camera to another field and, in 2 of the patients there probably was some error in calculating the depth of the distance to which the camera was inserted.

In this study, the combined gastroscopic and gastrophotographic examinations proved to be of diagnostic aid. In doubtful cases in which a definite clinical or Roentgen ray diagnosis could not be made, the additional diagnostic data were very valuable. Gastrophotography also served as a check on gastroscopy and the gastroscopist. The actual part seen was recorded and therefore any discrepancy in the preoperative and postoperative findings could not be ascribed solely, to the gastroscopist's interpretation, but also to the limitation of the procedure, as was illustrated in the above case report and Figure 3.

At the present time the subject of chronic gastritis is a controversial issue. Schindler has repeatedly emphasized its clinical importance and recently has published his histopathologic study on this subject.[5] Ruffin,[4] again, stated that chronic gastritis is an uncommon affection which does not give rise to a recognizable clinical picture. Therefore, if we can obtain gastrophotographs in conjunction with the gastroscopy, then it may be possible to obtain more unanimity as to what is the endoscopic picture of gastritis. A photographic record of the gastroscopic findings will be much more convincing than the interpretation of different gastroscopists looking at similar fields.

The importance of seeing the gastric wall before photographing it, the avoidance of blind photography, cannot be overemphasized. This was illustrated in the following case:

Case Study. E. S., 43 years old, had a gastric ulcer and lues. By gastroscopy, whitish areas which at first could not be identified, but which looked like barium sulfate particles, were seen adherent to the mucous membrane in the various parts of the stomach. A gastrophotograph of these whitish areas was obtained. It seems that the patient had been Roentgen rayed 2 days before the gastroscopy. The intern was instructed to lavage the patient's stomach, before the endoscopic examination, but forgot to do it. Hence, there was still barium in the stomach. This gave the photographic impression that a widespread tumor was present. If we had looked at the photograph, without seeing the gastric wall, before the picture was taken, an erroneous photographic diagnosis of malignancy could have easily been made, especially since the Roentgen ray examination showed a large gastric ulcer, in which the possibility of malignancy could not be ruled out.

Summary. Gastroscopy with the flexible instrument, in conjunction with gastrophotography in natural colors, was utilized in 41 patients. In 26 (63.4%), the photographs actually depicted what was seen endoscopically. This comparatively combined safe examination serves as a record of the gastroscopic findings, which enhances the endoscopic examination on one hand, and illustrates its limitations on the other.

REFERENCES

1. MAHER, M. A., ZINNINGER, M. M., SCHIFF, L., and SHAPIRO, N.: Am. J. Med. Sci., 205, 323, 1943.
2. RAFSKY, H. A.: Rev. Gastro-enterol., 9, 202, 1942.
3. RAFSKY, H. A.: Am. J. Digest. Dis., 9, 414, 1942.
4. RUFFIN, J. M.: Am. J. Digest. Dis., 9, 415, 1942.
5. SCHINDLER, R., and ORTMAYER, M.: Am. J. Digest. Dis., 9, 411, 1942.

BLOOD STUDIES IN THE AGED

PART II.   THE LEUKOCYTES IN THE AGED MALE AND FEMALE

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IN Part I of this study, we reported our findings regarding the various hematologic constants in which the erythrocytes were concerned in normal subjects past the age of 65 years. The present study treats the observations made upon a group in the same age range and reporting the total and differential leukocyte counts.

Experimental Study. The same individuals that were described in Part I of this study were used, with the leukocyte counts being done simultaneously with the erythrocyte studies. For the enumeration of the total number of white cells, a Spencer "Bright-line" Hemocytometer was used, which had

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been certified by the U. S. Bureau of Standards, the blood having been diluted in a certified pipette. As the diluting fluid, a 2% solution of acetic acid colored slightly with methyl violet was used. Counts were made in duplicate from each of the two certified pipettes and averaged.

The differential counts were done on blood smears which had been made on glass slides that were kept in chromic acid mixture, washed in distilled water, rinsed in alcohol, and dried over a hot plate. The smears were air-dried, and stained with Wright's stain for 1 to 2 minutes after which a buffer solution of phosphates at pH 6.7 was added until a metallic scum formed upon the surface of the stain. This was permitted to stand for 5 or 6 minutes and then poured off. The slides were then washed with water and air-dried. A total of 500 leukocytes were observed in different sections of the smear and the per cent of each type calculated.

The results of both the total leukocyte counts and the differential counts are to be seen in Table 1.

TABLE 1.—AVERAGE DETERMINATIONS OF TOTAL LEUKOCYTE AND DIFFERENTIAL BLOOD GROUPS BY AGE GROUPS

Age group	No. in group	WBC range in thous.	Av. WBC	Neutrophils				Av. lymphos.	Av. monos.	Av. eos.	Av. basos.
				Av. meta-myelo-cytes	Av. stab forms	Av. 2-lobed forms	Av. seg-mented forms				
				MALES							
65–69	4	5.4–10.2	7.92	0.2	3.5	10.3	49.0	35.2	0 7	0.6	0 5
70–74	6	7.6–11.8	9.16	0.2	6.2	7.5	48.5	34.4	1.6	1 1	0.5
75–79	20	5.0–10.7	7.34	0.3	4.1	6.5	54.0	31.5	1.7	1.4	0.5
80–84	13	7.2–10.2	8.57	0.0	5.3	5.5	50.4	35.2	2.0	1.3	0 3
85–89	5	5.1–10.3	8.30	0.0	2.8	9.6	55.4	28.8	2.0	1.0	0 4
90–94	2	8.7–12.0	10.40	0.0	7.5	7.5	53.5	25.5	1 5	3.5	1 0
				FEMALES							
65–69	4	5.9– 9.0	7.60	0.0	4.8	4.6	51.7	36.0	1.2	1.2	0 5
70–74	7	6.6– 9.1	7.74	0.1	2.4	4.0	57.6	33.3	1.1	1 0	0.5
75–79	28	6.2–11.1	8.41	0.1	4.0	8.5	49.6	33.8	2.0	1.6	0.4
80–84	3	5.0–10.2	7.23	0.3	3.0	5.3	56.2	32.3	1.6	1.0	0.3
85–89	4	7.9–11.0	9.12	0.0	4.7	4.5	51.0	37.0	1.2	1.4	0 2
90–95	3	6.0– 8.4	7.43	0.0	2.6	8.6	51.5	33.8	2.1	1 1	0 3
104	1	...	6.85	1 0	0.0	13.0	52.0	31.0	1.0	2 0	0 0

Discussion. Total white blood counts and differential leukocyte counts were performed on a group of 100 normal aged men and women. Values for the total leukocyte counts for the males ranged from 5000 to 12,050 per c.mm. (mean value, 8330 cells per c.mm.), while for the females the maximum and minimum values for the total leukocyte counts were 11,100 and 5050 respectively (average 8170 cells per c.mm.).

Miller,[3] in 1939, studying 160 men past the age of 60 years and assumed to be normal, found the total white blood cell count to have varied from 4000 to 13,000 cells per c.mm. (average, 7700). (Unfortunately the same type of study was not done by this author for females.)

Values for the total leukocyte counts in normal young adults may be considered to lie between 5000 and 10,000 cells per c.mm.[7] Since 98% of our total counts as well as the majority of those of Miller fall within these limits, we may assume that the total number of leukocytes in the circulating blood does not vary beyond physiologic diurnal

variation at the individual ages. It may be seen from Table 2 that the average values for the differential counts likewise seem to fall within the commonly accepted physiologic normal values.

For young adults, however, Osgood[5] reported that lymphocytes average 37.8%. Dobrovici[1] reported 20% lymphocytes and 5.4% monocytes in studying the blood of 11 persons from 67 to 81 years of age, while Étienne and Perrin[2] found the lymphocyte and monocyte percentages to have been 24.8 and 5.7 respectively in 27 persons past 80 years of age. Our lymphocyte counts average somewhat higher than these values, namely 33.6%. The percentage of monocytes (2.2%) in our subjects was found to be lower than the values reported by the aforementioned 2 writers.

Referring to Table 2, it may be seen that although there is a difference in the mean values for the various findings between the males and the females, it is only in the case of the total white counts that this difference becomes statistically reliable. The difference between the means divided by the square root of the sum of the squares of the probable errors is greater than 6 only in this case. (The value "6" represents the minimum value for truly significant differences.[6])

TABLE 2.—AVERAGE VALUES AND COMPUTATION OF STATISTICAL DIFFERENCES BETWEEN MALES AND FEMALES

	Mean value, male	Mean value, female	σ, male	σ, female	P.E., male	P.E., female	$\dfrac{M_M - M_F}{\sqrt{PE_M{}^2 + PE_F{}^2}}$
Total leukocytes per c.mm.	8330	8170	1600	1355	1078	911	13.50
Stab forms	5.3	4.2	2 8	2.4	1.90	1.6	0 36
Two-lobed forms	7.5	7 7	3.0	3 8	2 04	2 5	0 62
Mature polymorphonuclear neutrophils	52.7	5 3	4 7	1 4	3 20	1 0	0 89
Lymphocytes	33.5	33.8	6 4	6 5	4.30	4.4	0.49

P.E. = Probable Error.
σ = Standard Deviation.
M_F = Mean Female Value.
M_M = Mean Male Value.

$$\dfrac{M_M - M_F}{\sqrt{PE_M{}^2 + PE_F{}^2}} = \text{Criterion for significant difference.}$$

Thus it may be concluded that aged females, in general, have a total white blood cell count that is slightly lower than that of aged males. The distribution of the various types of leukocytes in the peripheral blood of males is not materially different from that shown by females in the same age group. Furthermore, the normal values reported in the literature as well as in the textbooks for young adults seem to hold for the case of aged individuals.

Conclusions for Part II. 1. Total leukocyte counts and differential counts were performed on a group of 50 normal aged males and 50 aged females.

2. The females showed a statistically reliable difference in the total leukocyte counts from those of the males.

3. The differential blood counts of the males and the females showed no reliable differences.

4. The values reported elsewhere for normal values in younger adults may be assumed to hold for the case of aged individuals.

REFERENCES

1. Dobrovici, A.:   Compt. rend. Soc. de biol., 56, 970, 1904.
2. Étienne, G., and Perrin, M.:   Compt. rend. Soc. de biol., 65, 250, 1908.
3. Miller, I.:   J. Lab. and Clin. Med., 24, 1172, 1939.
4. Newman, B., and Gitlow, S.:   Am. J. Med. Sci., 205, 677, 1943.
5. Osgood, E. E.:   Arch. Int. Med., 56, 849, 1935.
6. Pearl, R.:   Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, pp. 294, 376, et seq., 1940.
7. Stitt, E. R., Clough, P. W., and Clough, M. C.:   Practical Bacteriology, Hæmatology and Animal Parasitology, Philadelphia, P. Blakiston Son & Co., Inc., p. 331, 1938.

THE EFFECT OF MYXEDEMA UPON HEMOPOIESIS IN LEUKEMIA AND RELATED DISORDERS

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There are many publications dealing with the rôle of the thyroid in erythropoiesis. It has been shown[3,9,10,17] that anemia is a frequent finding in myxedema; and there is abundant evidence[6,18] to indicate that the abolition of the thyroid gland depresses erythropoiesis. The reports of the effect of thyroid on myelopoiesis and lymphopoiesis are scanty. In 1934 Dameshek[2] described the improvement in a case of chronic lymphatic leukemia after total thyroidectomy. The following year Witts[19] reported that total thyroidectomy produced no beneficial clinical or hematologic change in chronic lymphatic leukemia. It therefore seemed advisable to investigate the effects of myxedema on hemopoiesis.

Clinical Material and Methods. The cases studied included polycythemia vera (2 cases), erythroleukemia (3 cases), chronic myeloid leukemia (2 cases) and chronic lymphatic leukemia (2 cases). Of this series, 3 cases were considered unsuitable for study because of the short postoperative survival periods.

A complete hematologic survey, including sternal bone marrow examination, was made in each case prior to and after removal of the thyroid. The method used for obtaining and studying these marrows is described by Limarzi.[7] The basal metabolic rate, blood volume estimations and blood chemistry including cholesterol, calcium, phosphorus, serum proteins and uric acid were taken before and repeatedly following thyroidectomy.

All thyroidectomies were performed by the same surgeon (L. S.). After operation the patients were allowed to develop a myxedematous

state as demonstrated by dry, coarse skin, puffiness, heat intolerance, depressed basal metabolic rate and elevated blood cholesterol.

Polycythemia Vera and Erythroleukemia. A case of polycythemia vera previously reported[8] has been followed for the past 7 years. Prior to thyroidectomy the patient's complaints were headache, dizziness, fulness in the head, flushing of the face with cyanosis of the lips, hands and face, weakness, dyspnea, nausea and occasional attacks of vomiting. Headaches persisted for a few months after surgery. Within 3 months she commenced to develop signs and symptoms of hypothyroidism. Two years after the removal of the thyroid this patient presented all the findings of myxedema. The basal metabolic rate was -28%, blood cholesterol -250 mg. per 100 cc. blood and she complained of marked fatigue, edema of the eyelids and ankles, dry, thick skin and a persistent sensation of coldness.

It will be noted (Table 1) that the blood picture has changed markedly. The hemoglobin, erythrocytes and hematocrit have dropped to less than half of the preoperative values. The total blood volume has decreased from 10,706 to 3790 cc. The mean corpuscular volume has increased to 103.7 cu.μ and the mean corpuscular hemoglobin to 36.1 $\mu\mu g$. Thus, we are now dealing with a macrocytic, hyperchromic anemia. The leukocytes, differential blood pattern (Table 2) and platelets were not appreciably altered.

The bone marrow in polycythemia vera reveals a hyperplasia of all the cells. Qualitatively there is a marked erythroid immaturity and normal myeloid and megakaryocytic elements. Following thyroidectomy there is a quantitative decrease in the number of marrow cells while qualitatively the bone marrow is unchanged.

The patient was then placed on thyroid extract. During the next 4 years she was reasonably free of her preoperative symptoms. However, she then began to experience recurrence of headaches and dizziness, and examination of the blood showed a hemoglobin of 17 gm. and an erythrocyte count of 7,800,000. Her symptoms were relieved by repeated venesections. Since then she has taken thyroid extract intermittently and has been able to pursue her routine duties. At times the myxedematous symptoms become pronounced because of failure of the patient to adhere to the dosage of thyroid extract recommended.

Three cases of erythroleukemia were studied. All of the patients presented similar hematologic findings, namely, increased hemoglobin, erythrocytes and leukocytes, and an immaturity of the granulocytes (Tables 1 and 2). In erythroleukemia, which is probably a variant of myeloid leukemia with the added feature of erythremia, the sternal marrow presents a quantitative increase in all cells with a marked myeloid immaturity by virtue of many more neutrophilic myelocytes and myeloblasts than is usually seen in cases of chronic myeloid leukemia or polycythemia vera. There is a marked erythroid immaturity and a pronounced increase in the number of megakaryocytes in various phases of development. After removal of the thyroid, two of the cases of erythroleukemia responded with a considerable depression

TABLE 1.—BLOOD AND LABORATORY FINDINGS BEFORE AND ...

Cases	Hemoglobin (gm.)	Erythrocytes (mill.)	Hematocrit (%)	Mean corpuscular volume (cu.µ)	Mean corpuscular hemoglobin (µµg.)	Platelets (number)	Total blood volume (cc.)	B.M.R. (%)	Blood cholesterol (mg./100 cc.)	Date of thyroidectomy
Polycythemia vera (E. A.)										
Before (8/5/35)	21.5	8.62	79.0	92.0	24.8	Normal	10,706	+33	119	8/16/35
After (9/3/37)	11.5	3.18	33.0	103.7	36.1	Normal	3,790	−28	250	
Erythroleukemia (N. A.)										
Before (5/13/39)	19.2	6.30	55.0	87.0	30.0	Normal	5,816	+42	151	5/15/39
After (3/15/40)	17.5	5.46	55.0	101.0	32.0	Normal	7,149	−12	200	
Erythroleukemia (J. K.)										
Before (1/23/38)	22.0	7.75	74.0	95.4	28.4	Normal	9,233	+40	122	2/9/38
After (5/26/38)	16.5	4.26	47.0	110.0	38.0	Reduced	8,711	− 5	147	
Erythroleukemia (K. H.)										
Before (7/22/36)	14.2	7.56	52.0	68.7	18.7	Increased	4,982	+51	139	8/17/36
After (9/24/37)	8.0	3.57	28.5	80.0	22.0	Markedly increased to normal	4,020	−12	250	
Chronic myeloid leukemia (A.S.)										
Before (4/9/38)	15.0	4.68	44.5	93.0	32.0	Normal	...	+28	149	4/18/38
After (3/23/39)	7.8	2.62	27.0	103.0	29.0	Reduced	...	− 6	226	
Chr. lymphatic leukemia (L. N.)										
Before (9/3/38)	10.0	4.09	32.0	80.0	24.2	Normal	...	+35	200	9/15/38
After (8/7/40)	6.7	2.58	16.0	61.0	26.0	Markedly reduced	...	+11	217	

TABLE 2.—LEUKOCYTES AND DIFFERENTIAL BLOOD PATTERN (%) BEFORE AND AFTER TOTAL THYROIDECTOMY

Cases	Leukocytes (thous.)	Myelo-blasts	Myelo-cytes	Metamye-locytes	Stab forms	Neutro-phils	Eosino-phils	Baso-phils	Lympho-cytes	Mono-cytes	Reticulo-cytes (%)	Date of thyroid-ectomy
Polycythemia vera (E. A.)												
Before (8/5/35)	6.7	..	..	..	..	78	..	..	20	2	0.8	8/16/35
After (9/3/37)	5.0	..	..	..	..	64	4	3	25	4	1.5	
Erythroleukemia (N. A.)												
Before (5/13/39)	25.5	..	6	5	26	37	9	10	6	1	1.9	5/15/39
After (3/15/40)	43.0	1	10	9	49	9	7	9	4	2	2.0	
Erythroleukemia (J. K.)												
Before (1/23/38)	15.0	..	..	9	..	69	3	2	15	2	3.2	2/9/38
After (5/26/38)	39.0	..	3	15	10	57	2	1	11	1	3.5	
Erythroleukemia (K. H.)												
Before (7/22/36)	21.2	..	..	..	10	80	..	..	5	5	1.5	8/17/36
After (9/24/37)	17.5	..	..	1	34	41	..	3	16	5	0.6	
Chr. myeloid leukemia (A.S.)												
Before (4/9/38)	115.0	4	23	31	15	33	2	2	3	2	1.0	4/18/38
After (3/23/39)	33.1	8	31	14	..	17	3	7	2	3	2.8	
Chr. lymphatic leukemia (L. N.)												
Before (9/3/38)	150.0	..	..	..	..	6	1	..	91	2	0.5	9/15/38
After (8/7/40)	400.0	..	..	..	..	2	1	..	97	...	0.5	

of the hemoglobin and erythrocytes. The third case (N. A.) did not show much change in the hemoglobin and erythrocyte estimations in spite of an existing myxedema. In 2 of the patients (N. A. and J. K.) the anemia was macrocytic and hyperchromic in character. Post-operatively all of the cases showed a progressive leukocytosis and immaturity of the granulocytes, many normoblasts and a variable change in the number of blood platelets.

Before surgery the patient (K. H.) had platelet counts in excess of 1,000,000. These platelets presented alterations in size and shape. The removal of the thyroid induced a "megakaryocytic crisis" in the bone marrow manifested by a rise in the platelet count to 2,500,000 with abnormalities in size and shape of the platelets and megakaryocytic elements in the peripheral blood. Three years after operation normal platelet counts were obtained. Except for a moderate decrease in the number of immature erythroid cells the bone marrow remained unchanged.

Chronic Myeloid Leukemia. A case of chronic myeloid leukemia, was followed for 1 year after thyroidectomy. Hemoglobin and erythrocytes (Table 1) decreased progressively and 10 months postoperatively they were approximately half of the initial counts. The mean corpuscular volume increased from 93 to 103 cu.μ. The total white cell count dropped from 145,000 to 90,000. Because of progressive enlargement of the spleen several Roentgen ray treatments were administered. Following this, white cell counts of 33,000 to 50,000 were obtained. The differential blood smear (Table 2) prior to removal of the thyroid was typically that of chronic myeloid leukemia (myelocytic-metamyelocytic). The immaturity increased during the remainder of the follow-up study.

The bone marrow in chronic myeloid leukemia consists of an uncontrolled hyperplasia of normal appearing myeloid cells with a depression of erythropoiesis and megakaryopoiesis. Following thyroidectomy, the myeloid immaturity in the bone marrow was increased. The erythroid and megakaryocytic elements were greatly reduced.

Chronic Lymphatic Leukemia. A man with chronic lymphatic leukemia was under observation for 2 years after removal of the thyroid. An appreciable diminution in the hemoglobin and erythrocytes was obtained at this time. The total white cell count had increased from 150,000 to 400,000 with no essential alteration in the differential blood pattern.

The sternal marrow in chronic lymphatic leukemia is overrun by large numbers of small lymphocytes, similar to those seen in the peripheral blood. There is an almost complete disappearance of nucleated red cells and megakaryocytes. Complete ablation of the thyroid gland does not produce any significant change in the bone marrow.

Additional Laboratory Findings. A gastric analysis before removal of the thyroid and after development of myxedema was performed in 3 of the cases (E. A., J. K., K. H.). No significant difference in the

degree of acidity was noted.   In 2 of the cases studied, the absence of free acid was determined even after histamine stimulation.

Except for the cholesterol the blood chemistry was not appreciably changed.   In all cases the blood cholesterol (Table 1) was found to be increased after surgery.   Two of the patients exhibited symptoms and findings of postoperative tetany with blood calcium values of 5.5 and 6 mg. per 100 cc. of blood.

Discussion.   In a comprehensive review of the literature on the peripheral blood in thyroid disturbances, Bomford[1] is of the opinion that the anemia in myxedema is a physiologic adaptation on the part of the red cell to a diminished need of the tissues for oxygen.   He points out that the anemias found with myxedema can be divided into 3 types, (1) hyperchromic macrocytic, (2) hypochromic and (3) Addisonian hyperchromic.   Following total thyroidectomy for the treatment of congestive heart failure and angina pectoris, Stern and Altschule[16] noted the development of a macrocytic, hyperchromic anemia.   Jones[5] in a study of the sternal bone marrow in myxedema and hyperthyroidism found a normocytic, hypochromic anemia in his series of hypothyroid cases.   Sharpe[15] working with thyroidectomized rabbits obtained an anemia characterized by a definite macrocytosis and hyperchromia.   This change was not found clinically and the author believes this discrepancy may be due to the amount of functioning thyroid tissue in the spontaneous cases of myxedema.   Kunde, Green and Burns[6] produced experimental cretinism in rabbits by total extirpation of the thyroid.   Four to 6 months after thyroidectomy a macrocytic anemia was found.

Of the 6 patients in this series completely studied, 4 developed a macrocytosis.   Three of these cases had an associated hyperchromia. A microcytic, hypochromic anemia was observed in a case of erythroleukemia and in chronic lymphatic leukemia.   The macrocytosis found postoperatively is similar to the results of Sharpe,[15] Stern and Altschule,[16] and Kunde, Green and Burns.[6]   The macrocytic anemia or macrocytosis following thyroidectomy in these hemopoietic disorders was not associated with a megaloblastic bone marrow nor with a megalocytic, pernicious anemia blood pattern peripherally.

The induced myxedema did not influence the leukocytes or the blood pattern in polycythemia vera.   Increased leukocyte counts and a greater immaturity of the granulocytes were found after thyroidectomy in erythroleukemia.   It is sometimes difficult to distinguish between erythroleukemia and polycythemia vera.   The erythremia, leukemic blood picture, thrombocythemia with atypical blood platelets and megakaryocytic elements and the leukemic involvement of the spleen, liver and lymph nodes serves to separate these cases from polycythemia vera.   Occasionally cases of polycythemia vera with an overactivity of the leukogenic and megakaryogenic tissues may result in granulocytic immaturity and an increased number of normal and atypical platelets and megakaryocytic elements in the peripheral blood. A number of authors[11] have expressed the opinion that leukemia and

polycythemia vera are related diseases. On the other hand Naegeli[12] considers cases of erythremia which subsequently show signs of myelogenous leukemia as examples of myeloid leukemia at a stage before anemia has appeared. Harrop[4] and Reznikoff, Foot and Bethea[14] believe that polycythemia vera and leukemia are not related disorders.

In contrast to the report of Dameshek[2] the case of chronic lymphatic leukemia followed in this series did not benefit by total removal of the thyroid. The anemia became more profound, the leukocytes increased approximately 3 times their initial number and the differential did not change appreciably.

Naegeli[12] considered leukemia to be a disease produced by hormone disturbance. According to Oswald[13] no gland of internal secretion, however greatly disturbed, shows a blood picture which might even resemble leukemia. From the results of this investigation it would seem that the leukemic processes (myeloid and lymphatic) were not affected by total thyroidectomy. The case of myeloid leukemia survived for 1 year after surgery and the clinical and hematologic pictures with the exception of the myxedema did not appear to differ from that observed in the usual course of leukemia.

Conclusions. 1. Erythropoiesis is depressed in polycythemia vera after a total thyroidectomy and development of myxedema. The anemia is macrocytic and hyperchromic in type. Leukopoiesis is unaffected.

2. In erythroleukemia, myxedema induced a moderate to marked depression in erythropoiesis. The anemia is macrocytic or microcytic in type. There is a stimulation of leukopoiesis. In 1 case, after thyroidectomy there was early a "megakaryocytic crisis" followed later by normal platelet counts.

3. Hemopoiesis in chronic lymphatic and chronic myeloid leukemia is not altered by an induced myxedema.

REFERENCES

1. BOMFORD, R.. Quart. J. Med., 31, 495, 1938.
2. DAMESHEK, W., BERLIN, D. D., and BLUMGART, H. L.   New England J Med. 210, 723, 1934.
3. EMERY, E. S., JR.: Am. J. Med. Sci., 165, 577, 1923
4. HARROP, G. A., JR.: Medicine, 7, 291, 1928.
5. JONES, R. M.: Am. J. Med. Sci., 200, 211, 1940
6. KUNDE, M., GREEN, M., and BURNS, G.: Am. J. Physiol , 99, 469, 1931-32
7. LIMARZI, L. R.: Illinois Med. J., 75, 38, 1939.
8. LIMARZI, L. R., KEETON, R. W., and SEED, L   Proc. Soc. Exp. Biol. and Med. 36, 353, 1937.
9. MACKENZIE, G. M.: J. Am. Med. Assn., 136, 462, 1926
10. MINOT, G. R.: Med. Clin. North America, 4, 1733, 1921
11. MINOT, G. R., and BUCKMAN, T. E.: Am. J. Med. Sci., 166, 469, 1923
12. NAEGELI, O. Blutkrankheiten und Blutdiagnostik, 4th ed., Berlin, J. Springer, 1931.
13. OSWALD, A.: Klin. Wchn-chr., 13, 681, 1934.
14. REZNIKOFF, P., FOOT, N. C., and BETHEA, J M   Am J. Med. Sci, 189, 771, 1935.
15. SHARPE, J. C.: Am. J. Med. Sci., 194, 382, 1937.
16. STERN, B., and ALTSCHULE, M. D.: J. Clin. Invest , 15, 633, 1936
17. STONE, C. T.: Ann. Int. Med., 11, 215, 1928.
18. TATUM, A.: J. Exp. Med., 17, 636, 1913.
19. WITTS, T. J.: Brit Med J , 1, 1143, 1935

AIR–BORNE CROSS–INFECTION IN THE CASE OF THE COMMON COLD

A Further Clinical Study of the Use of Glycol Vapors for Air Sterilization*

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By far the greater part of mild upper respiratory infections probably originate from a virus or from viruses as yet unidentified. For this reason, quantitative determinations under varying environmental conditions of the viricidal effect of glycol vapors upon these disease agents cannot as yet be carried out. However, an essential experimental approach to this problem can be made by investigations of the incidence of mild upper respiratory infections and particularly of the common cold in children confined to bed in a convalescent home under controlled conditions and with the addition of glycol vapor to the air. Such an approach, as outlined in a preliminary report[1] and as carried out at the Children's Seashore House, gave sufficiently encouraging results to warrant a further clinical study. The present report covers the incidence of mild upper respiratory infections over a longer period and with larger groups of children in the same institution under similar environmental conditions.

Clinical Material. In contrast to the preliminary study[1] in which propylene glycol was vaporized continuously in a single ward for a period of over 2 months, a suitable control ward being maintained without glycol vapor, the present study included 6 wards (i. e., 3 wards on each of 2 floors) of the convalescent home over a period from October 1, 1942, to April, 1943, inclusive. In addition to the separation of the children on the 2 floors, each ward on the same floor was separated from the others by long corridors. The wards on the upper floor, located directly above those on the lower floor, had the same size, shape, position, exposure, and window space as those on the lower floor. Although the children with a few exceptions were not allowed out of bed, thus preventing for the most part actual contact between them, the nurses and other personnel frequently visited from ward to ward on the same floor, although they rarely visited from one floor to the other. Toys and books were transferred at times, though not frequently, from bed to bed, inasmuch as some of the beds were placed in contiguous pairs and no particular effort was made to prevent this, except during respiratory episodes in individual patients. Parents and friends visited the patients usually over the week-ends, but such visits became less frequent during the period of the study as the ban on pleasure driving in automobiles became more strict. In addition, contacts

with family and friends almost ceased during the period of study from mid-January as the result of a quarantine against visitors from the Philadelphia area, where a small epidemic of smallpox occurred. This quarantine was apparently reflected in the incidence of respiratory infections in the control wards (Table 1). The majority of the children were convalescent from rheumatic heart disease, 45 in number, and from orthopedic conditions, 30; while the rest, 30, represented a variety of non-infectious conditions. The ages ranged from 3 to 15 years. The sexes were evenly distributed.

TABLE 1.—THE INCIDENCE OF RESPIRATORY INFECTIONS, CHILDREN'S SEASHORE HOUSE (1942–43)*

Period beginning	Ward						Total cases	
	2A	2B	2C	3A	3B	3C	Controls	Glycol wards
10/9† . . .	0	0	0	6	5	8	19	0
11/2‡ . . .	7	6	7	0	0	1	20	1
11/26† . . .	0	2	0	4	8	7	19	2
12/21‡ . . .	5	9	6	0	0	1	20	1
1/14† . . .	0	0	..	4	3	..	7	0
2/8‡ . . .	3	4	..	0	1	..	7	1
3/4† . . .	0	0	..	4	4	..	8	0

TOTALS AND AVERAGES

Ward condition	Total	Per 3-week period	Per week
Before quarantine	78	6 5	2 2
After institution of quarantine	22	3 6	1 2
Total without glycol vaporization . . .	100	5 5	1.8
Total during glycol vaporization	5	0 28	0 09

Method of Study. The study was divided into 3-week periods of vaporization, separated by 2 to 3 days with no vaporization. The vaporization was continuous for each period on the 3 wards of one floor, while the 3 wards of the other floor remained as a control. Following the 2- to 3-day interval between periods, the 3 wards which had been vaporized became the control wards and the 3 control wards of the previous period became the vaporized wards. Such alternation, with the 2- to 3-day intervals between, occurred throughout the length of the study. The number, nature, and severity of the respiratory infections were recorded during each 3-week period in the 6 wards. The interval of 2 to 3 days was arranged for the purpose of permitting a respiratory infection which was incubating from the previous 3-week period to occur before the succeeding 3-week period started. Such an incubating infection was far more likely to occur from the control than from the vaporized wards, and had the 3-week periods alternated without a 2- to 3-day interval, respiratory infections for which they could not have been considered responsible would have been tabulated as occurring in the vaporized wards.

The method of vaporization of propylene glycol differed from that previously described in that the heat for vaporization was supplied by a small radio resistance unit inserted directly into the propylene glycol which was maintained at a constant level.§ During the greater part of the study, electric fans were placed behind the units for better distribution of the vapor. Units

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* Only 3 of these respiratory infections represent a second infection in a child previously infected. The interval between the 2 infections was never less than 5 weeks.

† Glycol vaporized on 2d floor (Wards 2A, 2B, 2C).

‡ Glycol vaporized on 3d floor.

§ The temperature of the heated glycol was kept below 80° C. It is important to avoid high temperatures because of the possibility of producing toxic oxidation products of the glycol.

of this type with electric fans were arranged on stands at the mid-point of the end-walls of each room, approximately 3 feet from the ceiling.

Determinations of the concentration of propylene glycol vapor were made at regular intervals throughout the study[2] (Table 2). As in the previous report, the samples of air were obtained from various points in the room at approximately the level of the patients' heads. Table 2 also indicates the variation in the amount of propylene glycol at such points, with the electric fan both on and off. The amount of propylene glycol vaporized daily was 600 cc.

TABLE 2.—CONCENTRATION OF PROPYLENE GLYCOL VAPOR IN AIR—MG. PER LITER

I. Samples at random, vapor dispensed by fan:

.067	.059
.085	.078
.054	.064
.042	.088
.070	.074
.086	.060

Mean: .069

II. Samples at various parts of ward, without fan:

Near vaporizer	Middle of ward	Far end
.068	.096	.060
.080	.120	.058
.074	.090	.040
.088	.080	.038
.092	.109	.044
.018	.093	.047
Mean: .094	.081	.048

III. Samples at various times after cessation of vaporization:

Hours after cessation of vaporization	Location of sample taken	
	⅓ length of ward from vaporizer	⅔ length of ward
0	.072	.045
	.060	.055
1	.023	.022
2	.033	.020
3	.009	.008

Determinations also were made of the rate of disappearance of propylene glycol from the wards following the cessation of vaporization, in order to afford some general idea of the effect of the exchange of air in the rooms on the concentration of the vapor. Such determinations showed that at the end of 1 hour approximately half of the original concentration of vapor was present; at the end of 2 hours, approximately a quarter was present, and at the end of 3 hours approximately one-eighth was present (Table 2). These determinations were made under the ordinary conditions of activity in the wards and indicate that the turnovers of air were considerably fewer than those to be expected in a more active institution.

Sufficient concentrations of propylene glycol were thus maintained to insure a marked reduction over the entire study in the total bacterial plate counts of the vaporized wards as compared with the control wards (Table 3). In the final period of 3 weeks, triethylene glycol in the concentrations originally suggested by Robertson was vaporized in the 3 test wards. During this and the 2 preceding 3-week periods, 1 of the wards included in the study was closed, chiefly due to the quarantine of the Philadelphia area for smallpox. Such

closure eliminated 2 wards from the latter part of the study, inasmuch as another ward comparable to the closed ward had to be omitted from the final calculations of the incidence of respiratory infections for proper comparison. Triethylene glycol in the concentrations used resulted in an even greater reduction in the few bacterial plate counts made than that resulting from propylene glycol vapor, although the concentration of the latter was maintained at approximately 10 times that of triethylene glycol. Because of the greater heat of vaporization of triethylene glycol, the same apparatus for vaporization could be used for both vapors, with the resulting approximate ratio of concentrations mentioned. The amount of triethylene glycol could be calculated only roughly because of the lack of a satisfactory method of air analysis for the vapor. The temperature of the wards usually was within the range of 68° to 72° F. The relative humidity was not determined in the wards in the earlier periods of the study; while in the later periods it ranged from 30 to 35%. The study was started at a time when the windows were closed for the colder season and was stopped when the windows were again opened for the warmer season.

TABLE 3.—BACTERIAL PLATE COUNTS IN WARDS CONTAINING PROPYLENE GLYCOL VAPOR AND IN CONTROL WARDS

Colonies per Petri plate per hour		Colonies per Petri plate per hour (Cont'd)	
Control	Propylene glycol	Control	Propylene glycol
66	13	70	13
85	12	84	12
72	14	72	14
81	17	81	11
89	11	96	11
93	10	84	8
64	12	92	12
68	9	73	14
102	13	86	13
79	11	92	15
83	9	103	16
73	13	84	15
62	14	107	12
59	16	86	14
91	—	..	..
84	19	Mean: 81.3	13.4
68	9		

BACTERIAL PLATE COUNTS IN WARDS CONTAINING TRIETHYLENE GLYCOL VAPOR AND IN CONTROL WARDS

Colonies per Petri plate per hour			
Lower concentration		Higher concentration	
Control	Trieth. glycol	Control	Trieth. glycol
94	12	98	3
76	11	70	4
87	9	103	4
99	10	111	1
103	11	99	6
74	9	79	6
88	11	84	4
94	12	81	2
90	10	94	2
89	13	91	3
93	11	93	1
91		86	5
Mean: 89.5	10.6	91.1	2.94

Results. The criteria* used for respiratory infections were the same as indicated in the previous study,[1] with the exception that in a very few instances upper respiratory episodes were included which did not show fever.   All such non-febrile episodes were of the type considered to be common colds and were only included on the basis of unmistakably objective signs.   Table 4 indicates the total number of respiratory episodes and their division among the 4 categories, *i. e.*, common cold, pharyngitis or sore throat, otitis media, and tracheobronchitis.   The difference between the vaporized and the control wards is sufficiently striking to require no statistical support.   It will be noted that by far the greatest number of respiratory infections, 79, were classified as common colds.   In one of the wards in which a nurse was suffering from a severe common cold during a period of vaporization, only 2 children contracted what appeared to be the same disease, whereas in other instances in several of the wards acting at the same time as control wards without vaporization, common colds appeared to develop in considerable numbers from an infected nurse or from other infected children.   The period of quarantine due to the smallpox epidemic in the Philadelphia area started on about February 1.   Whether or not this was responsible for the lessening of the respiratory episodes following that date is not clear, and yet the association of the two events is sufficiently close to appear related.   The bacterial flora of the nasopharynx were not investigated, largely because there was no sharp epidemic of respiratory infections during the period of study.

TABLE 4.—THE DISTRIBUTION OF THE RESPIRATORY INFECTION
BY DIAGNOSIS

Type of infection	Number	
	Control	Glycol
Tracheobronchitis	12	0
Otitis media	2	0
Acute pharyngitis	7	2
Common cold	79	3

Discussion. The striking reduction in common colds in the wards vaporized with propylene glycol is clear-cut evidence of the air-borne spread of the causative agent or agents of the common cold under the environmental conditions of this convalescent home for children. It must be emphasized that the children, with few exceptions, were confined continuously to their beds and the opportunities for direct contact were infrequent.   Had direct droplet hits† from sneezing or coughing been factors in the spread of infections, a larger number of respiratory episodes would have been expected in the vaporized wards, since propylene glycol could hardly have prevented this mode of spread.

* A respiratory infection was defined as a clinically recognizable episode with some objective manifestation in addition to fever.   Thus a sore throat was included only if it showed an inflamed nasopharynx on examination; a "common cold," or painful ear was included only if a discharge or evidence of inflammation was present, and a cough was included only if productive.

† Obviously the differentiation between direct droplet hits and air-borne droplets cannot be sharp, but is a useful clinical distinction.

The lack of infections from direct droplet hits was also related apparently to the confinement of the children to their beds. A sufficient reduction in the number of cases of pharyngitis and bronchitis was noted in the vaporized wards to warrant the supposition that cross-infections by air-borne bacteria were also limited by the propylene glycol vapor although in the absence of nasopharyngeal cultures this must be considered conjectural. In the instance of 1 nurse who remained on duty in a vaporized ward while suffering from a severe common cold, the opportunities among the children for contact infection or infection from direct droplet hits were considerably increased and apparently resulted in 2 common colds among them. In these 2 instances, the possibility of air-borne cross-infection from the same nurses could not be entirely eliminated.

That sufficient propylene glycol vapor was continuously present in the vaporized wards to reduce markedly the air-borne infective agents is evident from the bacterial plate counts obtained throughout the study. Inasmuch as the virus agents of disease thus far studied have been found susceptible to higher dilutions of the glycol vapors than the bacterial agents, the assumption is warranted that the propylene glycol vapor in the concentrations used inactivated the air-borne agent or agents of the common cold. The relative humidity in the periods tested was near the lower effective range for the antibacterial activity of propylene glycol (35 to 40%). The bacterial plate counts demonstrated that this degree of humidity was sufficient for such activity.

The total daily amount of propylene glycol vaporized would have had to be considerably greater in order to maintain an effective concentration, had not the turnovers of air in the wards been relatively few, as demonstrated by the quantitative determination of propylene glycol over a period of several hours following the cessation of vaporization. The amount of vapor for the purpose desired was not only sufficient by direct analysis but also sufficient according to bacterial plate counts. The effectiveness of triethylene glycol for the prevention of cross-infections was not demonstrated statistically in this study, although the small amount of evidence, as shown in Table 3, was entirely favorable to its value, as also were the bacterial plate counts.

Summary.   Propylene glycol was vaporized in wards of a children's convalescent home in bactericidal concentration. The incidence of upper respiratory infection was compared in these wards with that in control wards and found to be much lower. The fact that the great majority of the upper respiratory infections in control wards were common colds provides additional evidence of the viricidal effect of propylene glycol vapor, and may give indirect evidence also of the air-borne transmission of the common cold.

REFERENCES

1. HARRIS, T. N., and STOKES, J., Jr.: Am. J. Med. Sci., 204, 430, 1942.
2. PUCK, T. C.: Science, 95, 178, 1942.
3. ROBERTSON, O. H., PUCK, T. T., LEMON, H. F., and LOOSLI, C. G. ⸻, 97, 144, 1943.

THE BONE MARROW OF NORMAL DOGS

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In a study of spontaneous lymphomas in dogs, it was necessary to develop a technique for repeated bone marrow studies in the living animal. A review of the literature disclosed no consistent methods or results which could be used for a standard. Alexandrov[1] employed Arinkin's[2] sternal aspiration method in the study of the bone marrow of 12 normal dogs, and calculated the percentage distribution of marrow cells. Stasney and Higgins[6] investigated the marrow of 35 apparently normal dogs immediately after death of the animals by making imprints and sections of the 7th right ribs and the proximal and middle portions of the right femurs. They found only slight variations in the cellular organization from the different sites selected, although their quantitative results differed from those of Alexandrov.[1] This was attributed to the fact that their animals were anemic as reflected by lowered peripheral red cell counts. Mulligan[4] examined paraffin sections and smears of the bone marrow in 35 normal living adult dogs and 4 puppies by resecting portions of the 10th, 11th and 12th ribs under nembutal anesthesia. The smears were made by expressing the marrow from the rib with bone forceps, emulsifying it with plasma from the same animal, and then spreading this mixture on glass slides. His results were similar to those of Alexandrov,[1] and this procedure was suggested for repeated bone marrow studies, as 12 biopsies may be done on an animal if the 7th, 8th and 9th ribs (which are easily accessible) are also used.

In evaluating these techniques for obtaining marrow, Arinkin's[2] aspiration method is the simplest and an unlimited number of successive biopsies can be made upon the same animal. We have applied this procedure successfully in young dogs of medium and large size, but difficulty was experienced in small dogs due to the narrow medullary cavity, and in older dogs due to an increase in density and thickness of the outer layer of compact bone. Ho, Chu and Yuan[3] described a rapid method for the diagnosis of canine leishmaniasis by aspiration of bone marrow from the crest of the ilium. We have used this site successfully in obtaining marrow from animals of all ages and sizes. In addition to greater accessibility, it has all the advantages of Arinkin's[2] method, as the sternal marrow in the dog can only be aspirated from the upper 4–5 segments.

Material and Methods. The bone marrow was obtained from 10 healthy male and female dogs of different breeds, ranging in age from 1 to 11 years, and which were free from internal and external parasites. The animals were privately owned, and unlike the usual laboratory dog, had been well-fed and not subjected to any previous operative or other experimental procedure.

Examination of the peripheral blood indicated hemoglobin, red, white and differential counts within the accepted normal ranges.

The ilium of the dog is nearly parallel with the median plane of the body. The outer gluteal surface of the wing of the ilium is concave and thin. It is expanded anteriorly to form the crest which is strongly convex, thick, rough and prominent. The wing is bounded dorsally by the tuber sacrale which is thickened and has 2 eminences, and ventrally by the tuber coxæ which has 2 prominences. The tuber sacrale and coxæ together with the crest join to form the outer border of the anterior portion of the ilium.

The technique for marrow puncture is as follows: The animal is held on its side by an attendant or is strapped to the table in that position. Local anesthesia is not required as very little pain is experienced, and it is unnecessary to clip or shave the hair from the intended puncture region. The skin and hair over that area are sterilized with any suitable antiseptic. The anterior border of the ilium is outlined with the fingers of one hand, and a sterile $1\frac{3}{4}$ inches long, 15 to 18 gauge Kaliski or similar type needle with attached stylet is inserted through the skin and muscles into the thickest portion of the crest. The needle is simultaneously pushed and rotated with a screwing movement until the medullary cavity is entered. Occasionally, entrance is recognized by a sudden "give," although this is not usual. When the marrow cavity has been penetrated, the stylet is removed and a dry 10 to 20 cc. syringe is attached to the needle and about 0.1 to 0.2 cc. of the marrow withdrawn. The needle together with the attached syringe is removed from the animal and the drop expelled on a clean glass slide. From this drop, white cell and megakaryocyte counts are done with the same technique as for the white cell of the peripheral blood. Thin smears are made on several clean glass slides and stained with Wright's or May-Grunwald-Giemsa as for peripheral blood smears. Five hundred nucleated cells are enumerated and the percentages estimated for the differential count from the stained smears.

Several precautions must be exercised in obtaining the marrow. Not more than 0.2 cc. should be withdrawn to avoid too great an admixture with blood. As a distinct "give" is usually not felt when the medullary cavity is entered, the needle can easily be pushed completely through the bone. To avoid this, the needle should be directed toward the thickest portion of the crest, the syringe attached to the needle frequently and the plunger withdrawn to determine entrance into the marrow cavity. The bone marrow of the dog coagulates very quickly, requiring rapid execution of the entire procedure. Anticoagulants are not recommended as the fragility of the cells may be increased and a greater number of unidentified cells obtained in the differential count. If the animal is obese, the $1\frac{3}{4}$ inch needle may be too short, so that a longer needle, 2 to 3 inches in length should be used.

Observations. The marrow cells of the dog are similar to those in man, and we have followed the classification of Vogel, Erf and Rosenthal[1] in the identification of the cellular constituents of the dog marrow. The results of the peripheral blood and marrow studies are recorded in Table 1. Our observations indicate that an average of 48.32% of the marrow cells are of the myeloid series distributed as follows: neutrophilic myelocytes (3.76%), non-segmented neutrophils (23.5%) and segmented neutrophils (18.5%). The myeloblasts, eosinophilic myelocytes and non-segmenters, eosinophils, basophils and heterophils together comprise 2.56%. The erythroid cells average 38.7%, of which the megaloblasts are 1.02%, erythroblasts 2.5% and normoblasts 35.18%. The remaining 12.98% consist principally of lymphocytes which total 9.8% leaving 3.18% for the other classified cells.

In stained marrow smears, occasional agranulocytic myelocytes and polynuclears occur, which are attributed to differences of maturation

TABLE 1.—PERIPHERAL BLOOD AND ILIAL BONE MARROW OF NORMAL DOGS

Description	Beagle M 3 yrs.	Cocker F 3 yrs.	Beagle F 1½ yrs.	Collie cross M 4 yrs.	Chow cross M 3½ yrs.	Wire-haired terrier M 11 yrs.	Cocker M 3 yrs.	Fox terrier M 3 yrs.	Beagle M 7 yrs.	Boxer M 7 yrs.	Aver.	Group aver.
Peripheral Blood												
Red cells per c.mm. × 1000	6440	7090	7440	6110	6340	5960	6900	6660	6850	6500	6629	
Hemoglobin (Newcomer method), gm. per 100 cc.	11.6	12.0	11.0	12.8	11.8	12.0	12.7	13.1	12.4	13.1	12.25	
White cells per c.mm. × 100	126	172	175	121	114	100	136	129	142	137	135	
Juvenile neutrophils	2.0	1.0	1.0		2.0	1.0	2.0	2.0	1.0		1.2	
Bands	5.0	8.0	2.0	3.0	6.0	4.0	4.0	2.0	3.0	4.0	4.1	
Segmented	69.0	78.0	66.0	68.0	59.0	64.0	63.0	71.0	68.0	64.0	67.0	
Eosinophils	3.0		7.0	5.0	4.0	5.0	3.0	4.0	3.0	5.0	3.9	
Basophils	1.0		1.0	1.0							0.3	
Lymphocytes	17.0	12.0	20.0	21.0	26.0	23.0	27.0	19.0	21.0	21.0	20.7	
Monocytes	3.0	1.0	3.0	2.0	3.0	3.0	1.0	2.0	4.0	6.0	2.8	
Normoblasts (No. per 100 white cells)		3.0	2.0					1.0			0.6	
Bone Marrow												
Cells per c.mm. × 1000	317	90	100	110	56	120	95	192	240	128	144	
Megakaryocytes per c.mm.	33	33	22	5	11	11	22	110	132	33	41.20	
Myeloblasts	1.6	0.2	0.2	0.6	0.6	2.0		0.2		0.4	0.58	
Myelocyte neutrophils	5.4	0.2	1.8	1.4	2.8	7.6	4.2	6.2	3.6	4.4	3.76	
Myelocyte eosinophils	0.8			0.2				0.6	0.2	0.8	0.26	
Non-segmented neutrophils	22.8	16.2	19.2	29.2	24.4	28.4	22.6	20.2	24.8	27.2	23.50	48.5
Non-segmented eosinophils	0.8									0.4	0.12	
Segmented neutrophils	17.4	19.0	20.0	23.2	29.6	14.6	16.8	13.0	12.4	19.0	18.50	
Segmented eosinophils	0.4	2.4		1.0	2.4	3.0	1.4	2.0	1.0	2.0	1.56	
Segmented basophils						0.2					0.02	
Heterophils	0.2			0.2							0.02	
Megaloblasts	2.0	0.2	0.4	0.2	1.8	1.8	0.2	2.8	1.0	1.6	1.02	
Erythroblasts	2.6	2.8	2.0	1.4	3.8	3.8	3.6	2.4	4.0	1.6	2.50	38.7
Normoblasts	37.0	46.6	38.8	26.4	22.8	29.4	39.8	39.2	43.8	28.0	35.18	
Lymphocytes	8.4	8.2	14.2	7.2	15.2	8.0	10.6	10.0	5.8	10.4	9.80	9.8
Pathological lymphocytes		0.2	0.2	0.2							0.04	
Monocytes	0.4	2.6	1.0	5.2	0.4	0.2	0.6	1.0	0.4	0.2	1.20	3.1
Monoblasts		1.0		0.4							0.14	
Plasma cells		0.6	1.2	2.0	0.4		0.2	0.6	1.0	2.2	0.82	
Hematogones			0.8	0.8	0.6	0.2		0.4	0.4	1.2	0.44	
Reticulo-endothelial cells	0.2		0.2	0.6	0.6	0.8		1.4	1.6	0.6	0.54	
Myeloid-erythroid ratio	1.18:1.00	0.76:1.00	1.00:1.00	1.98:1.00	2.53:1.00	1.59:1.00	1.03:1.00	0.94:1.00	0.86:1.00	1.73:1.00	1.36:1.00	

rate of the nucleus and cytoplasm.[7]   In addition to these agranulocytic forms, there are found granule-free myelocytes, non-segmented and segmented neutrophils that have matured equally as far as the nuclei and cytoplasm are concerned.   The criteria for their recognition depends on the nuclear and cytoplasmic characteristics.

TABLE 2.—COMPARISON OF PERIPHERAL BLOOD AND BONE MARROW DATA OF NORMAL DOGS REPORTED BY DIFFERENT AUTHORS

Peripheral blood	Alexandror	Stasney and Higgins	Mulligan	Present authors
Red blood cells per c.mm.	6,335,000	5,000,000	6,760,000	6,629,000
Hemoglobin	100%	No other	14.4 gm.	12.25 gm.
White blood cells per c.mm.	11,260	data	10,700	13,520
Metaneutrophils	0 17	given		1 2
Juvenile neutrophils	...		..	1 2
Stab neutrophils	..		4 2	4 1
Neutrophils	67 23		70 6	67 0
Eosinophils	3 48		4 1	3 9
Basophils	0 06			0 3
Lymphocytes	14 30		19 3	20 7
Monocytes	12 30		1 8	2 8
Smudge forms	1 30			
Türck cells	1 00			
Reticulo-endothelial cells	0 02			
Normoblasts (number per 100 white cells)	...	...	...	0 6

Bone marrow	Sternum	Rib	Rib	Ilium
Total white cells per c.mm.	.	.	.	141,860
Megakaryocytes per c.mm.				41 20
Myeloblasts	1 20	0 51		0 58
Leukoblasts	..	1 89		
Promyelocyte neutrophils	0 90	2 83	1 5	
Myelocyte neutrophils	1 20	8 93	4 7	3 76
Myelocyte eosinophils	0 50	1 15		0 29
Metamyelocyte neutrophils	6 70	15 29	10 5	
Metamyelocyte eosinophils	1 60			
Stab neutrophils			31 0	23 50
Non-segmented neutrophils				0 12
Non-segmented eosinophils				
Neutrophils	35 10		3 9	18 50
Eosinophils	1 32	2 85	3 7	1 55
Basophils	0 13	0 05		0 02
Granulocytes		5 06		
Heterophils		0 14		0 02
Megaloblasts				1 02
Proerythroblasts	1 90		0 5	
Erythroblasts	21 50		1 5	2 50
Normoblasts		58 98	35 1	35 18
Megakaryocytes	0 10	0 12		0 83
Lymphocytes	8 80	1 24	1 9	0 04
Pathologic lymphocytes				1 20
Monocytes	10 40			0 14
Monoblasts				0 82
Plasma cells				0 24
Reticulo-endothelial cells	5 10	0 90	0 6	
Stem cells				
Türck cells	0 30			0 44
Hematozones	2 60			
Smudge forms			2 1	
Unidentified cells				
Myeloid-erythroid ratio	2.68:1.00	0.63:1.00	1.96:1.00	1.50:1.00

The presence of occasional deep blue granules in eosinophilic myelocytes and non-segmenters has been described in man and dog.   There appear to be greater numbers of these cells when the smears are stained with May-Grunwald-Giemsa than with Wright's stain.

Comment.   Table 2 demonstrates a comparison of our quantitative data of the bone marrow and peripheral blood with that obtained by other investigators.   Although the data for the peripheral blood are very similar, this is not true for the bone marrow.   In addition to variations in nomenclature, there are differences in the quantitative percentages of the marrow cells.   The latter may be due to the animals used as, with the exception of our series, laboratory dogs were employed in all instances.

The myeloid-erythroid ratios in man, rat and the rabbit are greater than one.[6]   This is also noted in the dog, but in general there are greater numbers of erythroid cells as compared to myeloid cells than in man and rabbit.   The increase in cells of the erythroid series in the dog may be possibly due to the fact that the red cells of the peripheral blood occur in larger numbers, which might necessitate a greater erythroid activity to maintain the normal quota of erythrocytes in the circulating blood.

Reich and Kolb[5] in a recent quantitative study in man found considerable variations in multiple sternal marrow samples taken simultaneously.   These observations consequently cast doubt on the accuracy of total cell counts of the marrow.   Despite this criticism, we believe such examination aids in distinguishing hypoplastic from hyperplastic centers, particularly when care is exercised in aspirating not more than 0.2 cc. of marrow.

The technique of obtaining marrow from the crest of the ilium is of obvious value when repeated examinations are desirable.   The procedure is simple and lends itself to frequent observations of changes in the myeloid and erythroid tissue under normal, diseased and experimental conditions.

Summary.   1. A simple method suitable for repeated biopsies in obtaining bone marrow from the crest of the ilium in living dogs has been described.

2. Data has been given for 10 normal dogs concerning the total number of nucleated cells and megakaryocytes, and the percentage distribution of marrow cells of the ilial bone marrow.

REFERENCES

1. ALEXANDROV, A. P.:   Fol. hæmatol., 41, 428, 1930.
2. ARINKIN, M. I.:   Vestnik khir., 10, 57, 1927.
3. HO, E. A., CHU, H. S., and YUAN, I. C.:   Chinese Med. J., 58, 679, 1940.
4. MULLIGAN, R. M.:   Anat. Rec., 79, 101, 1941.
5. REICH, C. I., and KOLB, E. M.:   AM. J. MED. SCI., 204, 496, 1942.
6. STASNEY, J., and HIGGINS, G. M.:   AM. J. MED. SCI., 193, 462, 1937.
7. VOGEL, P., ERF, L. A., and ROSENTHAL, N.:   Am. J. Clin. Path., 7, 436, 1937.

THE TOXICITY OF PENICILLIN AS PREPARED FOR CLINICAL USE

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In the course of experiments on gas gangrene,[9] 7 guinea pigs which had been infected with *Cl. perfringens* and treated subcutaneously with penicillin died, although they had shown no symptoms of gas gangrene. They had received 2600 to 4000 Florey units (F.U.) per kg. per day in 7 doses daily for 3 to 4 days. Deaths occurred 12 to 72 hours after treatment had been stopped. The only signs of illness were extreme anorexia, ruffled fur, lethargy and loss of weight. At autopsy, no local or systemic evidences of gas gangrene were found, and no anaërobes were recovered in cultures, nor were there any findings suggesting death might be due to any spontaneous intercurrent infection. The amounts of penicillin given to these animals were well below the toxic level for other animals, but the possibility remained that guinea pigs are more susceptible to penicillin than other animals. To investigate this possibility, further experiments were undertaken.

Experiments. Penicillin used in these experiments was prepared from crude culture filtrates of *Penicillium notatum* grown on Czapek-Dox medium[3] modified by substitution of brown sugar for glucose.[7] Preparations Pooled Lot (100 F.U. per mg.) and Lot No. 27404 (90 F.U. per mg.) were sodium salts for clinical use prepared by Dr. J. C. Hoogerheide and Mr. C. W. Eberlein by extraction of the culture filtrate at pH 6.5 with butanol, replacement of the latter by benzene, the reëxtraction with bicarbonate followed by transfer, via ether, into phosphate buffer and finally into bicarbonate solution.[*] These preparations were actually used clinically. Preparation M501 (400 F.U. per mg.) was prepared by one of us (H.B.M.) from a product assaying 150 F.U. per mg. by a purification procedure involving selective reëxtraction from ether solution with pH 5 buffer, conversion into the sodium salt, precipitation of impurities with silver sulfate and preparation of the sodium salt from the material remaining in the supernatant solution. Preparation A572 (250 F.U. per mg.) prepared by Dr. A. E. O. Menzel, originated from a pool of preparations which had been purified by transferring into chloroform in the presence of ammonium sulfate at pH 4, extracting with buffer at pH 6, repeating the chloroform procedure and extracting with buffer at pH 5.5. The resultant buffer solution was transferred to ether and the sodium salt prepared by extraction with sodium bicarbonate.[*] Sodium salt M568 was prepared by

H. B. M. by the amyl acetate extraction procedure from a batch of deep culture filtrate. Further purification was effected by chromatographic methods.*

The activity of these preparations was determined by *in vitro* titration against a 6-hour culture of *Staphylococcus aureus* strain H.† Decreasing amounts of penicillin were placed in a series of 13 × 100 mm. tubes, the volume in each tube brought up to 1 ml. with broth and 1 ml. of a 10^{-6} dilution of the culture in broth added to each tube. The tubes were shaken and incubated at · 37° C. for 16 hours. The smallest amount of penicillin inhibiting growth as indicated by lack of any turbidity after shaking the incubated tubes was taken as the end-point and the number of Florey units per milligram determined by comparison with a standard preparation of penicillin simultaneously tested in the same way. The standard had been previously assayed by comparison with a standard preparation of known potency.‡² All penicillin was kept either dry or in aqueous solution at 1 to 3° C. under which conditions it was stable for the periods under observation. Both for intravenous and for subcutaneous injection the penicillin was prepared in distilled water.

Acute Toxicity of Penicillin. The comparative toxicity of penicillin given intravenously in a single injection to mice, guinea pigs and rabbits is presented in Table 1. All of the animals received the same preparation (Lot No. 27404) containing 90 F.U. per mg. The solutions contained no particles and were injected slowly to avoid reactions due to hypertonicity.

TABLE 1.—ACUTE TOXICITY OF PENICILLIN GIVEN INTRAVENOUSLY TO MICE, GUINEA PIGS AND RABBITS

(Penicillin Lot No. 27404 Containing 90 F.U./mg.)

Animals	Wt. (gm.)	Dose F.U.	F.U./kg.	Mg./kg.	Result
10 mice	20	1,395	69,700	774	No reaction
5 mice	20	1,800	90,000	1000	4 died in 4 hrs. 1 died in 5 days
1 mouse	20	2,511	125,000	1388	Sick, recovered
4 mice	20	2,790	139,000	1544	1 died in 30 min. 2 died in 16 hrs. 1 sick, recovered
Guinea pig:					
No. 179	225	4,185	18,000	200	No reaction
No. 180	211	5,580	27,900	310	No reaction
No. 181	178	5,580	31,300	347	No reaction
No. 185	230	12,370	53,000	588	Died in 93 hrs.
No. 186	214	12,370	57,000	633	Sick, killed in 9 days
No. 184	219	15,462	75,000	833	Sick, killed in 9 days
No. 183	217	15,462	75,000	833	Died in 2 min.
No. 182	305	30,925	101,000	1122	Died in 10 min.
Rabbit:					
No. 3	790	37,110	47,000	533	No reaction
No. 2*	770	55,665	70,200	780	Died in 72 hrs.
No. 1	1100	122,310	111,000	1233	Died in 1 hr.

* Coccidiosis possible cause of death.

The numbers of animals were too small to determine accurately the minimal fatal dose, and could not be increased because of lack of material. However, it is apparent from these experiments that, although the guinea pigs appear slightly more sensitive, there is no great difference in the susceptibility of mice, guinea pigs and rabbits to a single intravenous dose of penicillin. Also it is obvious that the acute toxicity

of penicillin is not very great. This is borne out by the reports of other workers. Chain, Florey, Gardner, Heatley, Jennings, Orr-Ewing and Sanders[2] found that 10 mg. intravenously had no effect on mice and rats, and that 40 mg. had no effect on the blood pressure, heart beat or respiration of a cat. They did not give the activity of their penicillin in Florey or any other units. Hobby, Meyer, and Chaffee[4] gave 32 mg. (1.8 gm. per kg.) as the L.D. 50 for 18 gm. mice, and reported no reaction in guinea pigs following the injection of 320 mg. (1.3 gm. per kg.), but they also did not give the potency of their penicillin or the number of animals used. Abraham, Chain, Fletcher, Florey, Gardner, Heatley and Jennings[1] were able to produce a severe reaction in mice by the injection of 20 mg. of a preparation containing 40 to 50 F.U. per mg., but Florey and Jennings[5] reported that 20 mg. of penicillin containing 250 to 325 F.U. per mg. could be given to 20 gm. mice without ill effects. This indicates that purification reduces the acute toxicity of penicillin. The results of the experiments reported here, in which only one penicillin preparation (90 F.U. per mg.) was used and a dose of 1 gm. per kg. produced severe reactions and death in mice and rabbits, are in agreement with those of Robinson[11] who produced 90% mortality with the intravenous injection of mice with 90,000 F.U. per kg. of a preparation containing 60 F.U. per mg., but with a preparation containing 400 F.U. per mg., deaths did not occur when the intravenous dose was below 600,000 F.U. per kg. In an experiment using small numbers of mice we obtained only slight reactions with 250,000 F.U. per kg. of a preparation containing 500 F.U. per mg.,[10] further indication that purification lowers the toxicity.

Toxicity of Multiple Subcutaneous Doses of Penicillin. In the experiments on treatment of gas gangrene with penicillin, the guinea pigs had received multiple doses subcutaneously. Therefore, the next experiment was designed to compare the reactions of guinea pigs, mice and rabbits to repeated subcutaneous injections of penicillin. Two guinea pigs and one rabbit received about the same dose per kg. of body weight and 6 mice about one-half this dose per kg. of the same penicillin preparation. The results are given in Table 2.

TABLE 2.—TOXICITY OF REPEATED SUBCUTANEOUS DOSES OF PENICILLIN FOR GUINEA PIGS, MICE AND RABBITS

(Penicillin Preparations Pooled Lot, 100 F.U. mg., Given 7 Times Daily)

Animal	Wt. (gm.)	Single dose F.U.	Penicillin per kg. per day	Total amount given	Result
Guinea pig: No. 149	278	500	12,500 F.U. 125 mg.	8,000 F.U. 80 mg.	Moribund 5 hr. after 21 dose
No. 150	283	500	12,500 F.U. 125 mg.	11,000 F.U. 110 mg.	Moribund 3 hr. after 22 dose
Rabbit: No. 37	870	1500	12,500 F.U. 125 mg.	31,000 F.U. 310 mg.	No reaction after 4 days treatment
Mice: Nos. 1 to 6	20	22.8	7,250 F.U. 72 mg.	205 F.U. 2 mg.	No reaction after 4 days treatment

Both guinea pigs receiving the pooled lot of penicillin lost weight and, when moribund, were killed to obtain fresh material for culture. The mice and rabbit remained normal throughout the experiment.

These results indicated that guinea pigs are more susceptible to continued subcutaneous injections of penicillin than mice and rabbits. However, since the penicillin available was relatively impure, it was possible that contaminating substances present were more toxic for the guinea pig than for the rabbit or the mouse.

In an attempt to determine whether further purification by different methods would alter the toxicity of penicillin for guinea pigs, 3 preparations of high potency were given subcutaneously over a period of several days. The amounts of preparations M591 (400 F.U. per mg.) and A872 (250 F.U. per mg.) were sufficient for only one animal on each preparation, and were given in 7 doses daily. Preparation M868 (1068 F.U. per mg.) was given 3 times daily. The experiment is summarized in Table 3.

TABLE 3.—TOXICITY FOR GUINEA PIGS OF REPEATED SUBCUTANEOUS DOSES OF MORE HIGHLY PURIFIED PENICILLIN

Animal	Wt. (gm.)	Penicillin preparation	Single dose F.U.	Penicillin per kg. per day	Total dose given	Result
No. 163	269	M591 400 F.U./mg.	400 changed to 200 on 3d day	11,500 F.U. 26 mg. 5,600 F.U.	7,000 F.U. 17 mg.	Moribund; killed on 4th day
No. 164	250	A872 250 F.U./mg.	500 changed to 250 on 3d day	14,000 F.U. 56 mg. 7,000 F.U.	8,750 F.U. 35 mg.	Died on 4th day
No. 295	240	M868 1068 F.U./mg.	550	7,000 F.U. 6.5 mg.	11,000 F.U. 10.3 mg.	Sick 3d and 4th day; recovered; marked local irritation
No. 296	330	"	750	7,000 F.U. 6.5 mg.	7,050 F.U. 6.6 mg.	Died on 4th day
No. 297	355	"	800	7,000 F.U. 6.5 mg.	14,400 F.U. 13.4 mg.	Died on 7th day
No. 298	310	"	700	7,000 F.U. 6.5 mg.	14,000 F.U. 13.1 mg.	Sick 3d and 4th days; recovered; marked local irritation
No. 299	265	"	850	7,000 F.U. 6.5 mg.	10,200 F.U. 9.5 mg.	Moribund; killed on 4th day

Only the higher potency material (M868) showed any decrease in toxicity. Two out of 5 guinea pigs given this preparation became sick on the 3d day, but by the 6th day were improving and ultimately survived. Because of the small number of animals used, these results may be due to chance alone, but it is also possible that this does indicate a decrease in toxicity with increased purification. Further experiments with highly purified material will be necessary to decide this point. The fact remains that even with a 10-fold increase in purity, penicillin was still toxic for guinea pigs.

For further comparative data on guinea pigs, mice and rabbits, a more extensive experiment was carried out in which different doses of penicillin were given subcutaneously over a period of several days. Some of these animals were those which had survived a single dose intravenously. Subcutaneous injections were begun 24 hours after the intravenous dose. In an attempt to produce toxic reactions in mice and rabbits similar to those seen in guinea pigs, 2 rabbits (Nos. 3, 4) and 6 mice were given doses 5 to 7 times greater per kilogram than the dose which produced toxic reactions in guinea pigs. All animals received the same preparation of penicillin (Table 4).

TABLE 4.—TOXICITY OF REPEATED SUBCUTANEOUS DOSES OF PENICILLIN FOR GUINEA PIGS, MICE AND RABBITS

(Penicillin Lot No. 27404 Containing 90 F.U./mg., Given 3 Times Daily)

Animal	Wt. (gm.)	Single dose F.U.	F.U. per kg. per day	Total amount given F.U.	Result
Guinea pig:					
No. 179*	215	500	7,000	6,500	Died 5th day
No. 180*	194	500	7,700	2,000	Died 2d day
No. 181*	174	500	8,600	4,000	Died 3d day
12 mice*	20	100	15,000	2,500	No reaction after 8 days treatment, killed on 9th day
6 mice	16	220	41,250	6,160	No reaction after 9 days treatment, killed on 9th day
Rabbit:					
No. 3*	780	12,220 changed to 3,375 on 4th day	47,000 15,000	143,855	No reaction after 7 days treatment, killed on 9th day
No. 4	710	14,200 changed to 3,375 on 4th day	60,000 16,000	200,000	No reaction after 7 days treatment, killed on 9th day

* See Table 1 for previous treatment of these animals. SC doses were begun 24 hours after IV doses

The mice showed no reaction, the guinea pigs lost weight and died, and the rabbits lost weight during the first part of the treatment period, but regained this loss during the latter part. This regain in weight was probably due to the reduction in dose of penicillin necessitated by lack of material. However, extreme caution is necessary in evaluation of loss of weight in relation to toxicity because of the possible rôle of chronic pneumonia or coccidiosis which occur all too frequently among normal guinea pigs and rabbits.

To exclude the possibility that toxicity is a property only of the penicillin prepared at New Brunswick, a sample of penicillin from another source* was tested in guinea pigs. Treatment and results are given in Table 5.

TABLE 5.—TOXICITY OF REPEATED SUBCUTANEOUS DOSES OF MERCK PENICILLIN FOR GUINEA PIGS

(Preparation Containing 150 F.U./mg., Given 3 Times Daily)

Guinea pig	Wt. (gm.)	Dose F.U.	F.U. per kg. per day	Total amount given F.U.	Result
No. 187	213	500	7040	2000	Died on 9th day
No. 188	207	500	7200	7200	Died on 5th day
No. 189	218	500	6880	7200	Died on 5th day
No. 190	200	696	7200	8352	sick, killed on 6th day
No. 191	273	655	7200	7500	Died on 9th day

Since 4 out of 5 of the animals died and the other was sick when killed, it was concluded that the toxic property of penicillin is not confined to our preparations.

Guinea pigs are unique among the common laboratory animals for their inability to synthesize vitamin C. This fact and the results of our experiments on toxicity of repeated doses of penicillin for guinea pigs suggested that there might be some connection between the metabolism of vitamin C and penicillin toxicity. All guinea pigs were

fed a balanced diet with liberal amounts of greens, and no gross evidence of scurvy was ever found in those dying of penicillin toxicity. However, in view of the reports that certain organic compounds caused an increase in the excretion of vitamin C in the rat and that administration of large amounts of vitamin C had a detoxifying action on benzene, lead and arsenic compounds, and on some of the bacterial toxins (see Rosenberg's monograph[12] and the review of Györgi[6]) it was decided to investigate the rôle of vitamin C in penicillin toxicity in guinea pigs.*

In one experiment, a group of 4 guinea pigs on a vitamin C deficient diet[4] was given 10 mg. of sodium ascorbate subcutaneously daily for 3 days before penicillin treatment, but none during such treatment. Another group of 4 on a vitamin C deficient diet were given 10 mg. of sodium ascorbate subcutaneously daily for 3 days prior to and during penicillin treatment, and a third group on regular diet with a liberal amount of greens were given no sodium ascorbate. Seven thousand F.U. of penicillin (134 F.U. per mg.) per kg. per day were given subcutaneously in 3 doses daily. At the time of death pieces of liver and the adrenals were weighed and placed in 5% metaphosphoric acid for determinations of ascorbic acid. The results are shown in Table 6.

TABLE 6.—THE EFFECT OF VITAMIN C ON THE TOXICITY FOR GUINEA PIGS OF REPEATED SUBCUTANEOUS DOSES OF PENICILLIN

(7000 F.U./kg. per Day of Penicillin M869 [134 F.U./mg.], Given 3 Times Daily)

Guinea pig	Wt.	Vitamin C treatment	Time of death after penicillin treatment began (day)	Ascorbic acid content	
				Liver (mg./gm.)	Adrenals (mg./gm.)
No. 300	203	10 mg. sodium ascorbate SC	2d	0.061	0.23
No. 301	237	daily for 3 days before peni-	7th		
No. 302	284	cillin treatment; no further	8th		
No. 303	270	vitamin C	5th		
No. 304	245	10 mg. sodium ascorbate SC	3d		
No. 305	239	daily for 3 days prior to and	8th		
No. 306	237	during penicillin treatment	12th		
No. 307	234		3d	0.15	0 47
No. 308	247	No sodium ascorbate; greens	Survived		
No. 309	272	included in diet	6th		
No. 310	224		3d	0.037	0.083
No. 311	267		6th		
No. 312	226	100 mg. sodium ascorbate for	3d		
No. 313	253	3 days prior to and during	4th	0.48	0.84
No. 314	234	penicillin treatment*	3d		
No. 315	230	No sodium ascorbate; greens	4th		
No. 316	303	included in diet*	2d		
No. 317			6th		

* On the 2d day of penicillin treatment preparation 29114, containing 99 F.U./mg., replaced preparation M869.

Although 10 mg. of sodium ascorbate a day was about 5 times the dose necessary to prevent scurvy and raised the ascorbic acid content of the liver and adrenals about 5 times over that of guinea pigs fed the regular laboratory diet, it did not protect the guinea pigs from the toxic action of the penicillin.

In another experiment, 3 guinea pigs on a vitamin C deficient diet were given 100 mg. of sodium ascorbate daily for 3 days prior to and

* We are indebted to Dr. Laslo Kajdi of the Department of Pediatrics, The Johns Hopkins Hospital, Baltimore, for suggesting that vitamin C might be connected with penicillin toxicity in guinea pigs and for the assays of ascorbic acid.

during penicillin treatment, and 3 guinea pigs on regular diet with greens were given no sodium ascorbate. Penicillin was given in the usual way (7000 F.U. per kg. per day). Two preparations were used, one containing 134 F.U. per mg., the other, 99 F.U. per mg. At the time of death, liver and adrenals were taken for ascorbic acid assay (Table 6) and sections were made of the costochondral junctions, the head of the tibia, and the lower jaw for detection of sub-clinical scurvy. Study of these microscopic preparations revealed no abnormalities.

Since all but one of the guinea pigs in both experiments died, in spite of the massive doses of vitamin C, it was concluded that vitamin C does not have a protective action on penicillin toxicity.

Pathologic Findings. Since the lesions found in each species of animals, regardless of dose of penicillin given, were approximately the same, the pathologic findings will be discussed together.

GUINEA PIGS. No lesions were seen in the gross or microscopically in the central nervous system, lung (with the exception noted below), spleen, lymph nodes, intestine, pancreas, kidney, adrenal, gonads or voluntary muscle except when the latter was subjacent to the site of inoculation.

Heart. In 12 instances, this organ was normal, but in 3 (G.P. 180, 181 and 299) there were lesions in the wall of the left ventricle consisting of necrosis of several muscle fibers and surrounding infiltration with monocytes and a few polymorphonuclear cells.

Site of Inoculation. In the gross, the area was edematous and yellowred in color when compared to normal subcutaneous tissue.

Microscopically the picture was one of edema of the subcutaneous tissue and infiltration, of greater or lesser degree, of this tissue with monocytes and some polymonuclear leukocytes (Fig. 3). In the majority of cases the damage extended into the subjacent voluntary muscles. Muscle fibers in varying degrees of destruction and phagocytosis were seen and there was considerable infiltration of cells of the same type as seen in the subcutaneous tissue.

In 1 case penicillin was accidentally administered into the lung by the trachea. A widespread acute pneumonic consolidation and fibrinous pleurisy resulted.

Liver. Foci of necrosis, often of considerable size, were present in many of the guinea pigs given penicillin. However, although liver damage was frequently observed, its importance in these animals seemed questionable and an exhaustive search was made for similar lesions in apparently normal animals. Six guinea pigs from each of the two sources from which the experimental animals were obtained, were killed and 6 pieces of liver taken from each animal. Foci of necrosis were present in 2 out of the 6 animals in one group and in 3 of these in the other group. In addition scars suggesting healed foci were found in 1 animal in each group.

RABBITS. No lesions were found in the central nervous system, spleen, lymph nodes, pancreas, liver, kidney, adrenal, gonads, heart or voluntary muscle.

Site of Inoculation. In the gross, the subcutaneous tissue was greatly thickened by edema and blood-tinged in color. Microscopically, the picture resembled that described for the guinea pigs, except in degree.
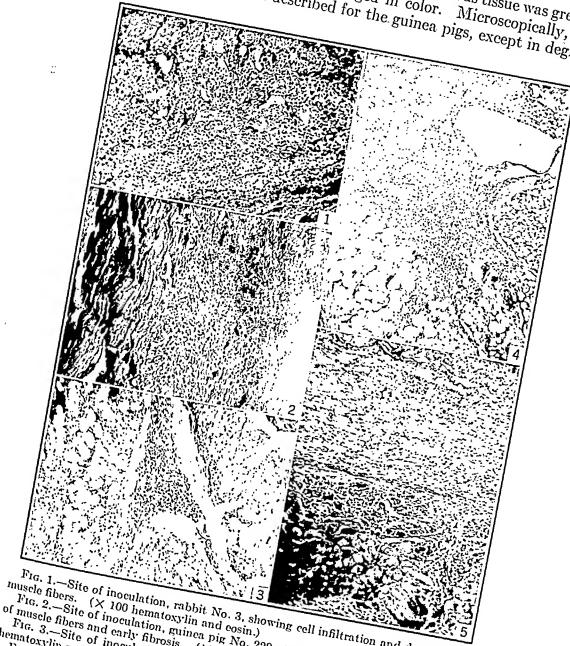
Fig. 1.—Site of inoculation, rabbit No. 3, showing cell infiltration and destruction of muscle fibers. (× 100 hematoxylin and eosin.)

Fig. 2.—Site of inoculation, guinea pig No. 229, showing cell infiltration, destruction of muscle fibers and early fibrosis. (× 100 hematoxylin and eosin.)

Fig. 3.—Site of inoculation, guinea pig No. 164, showing cell infiltration. (× 100 hematoxylin and eosin.)

Fig. 4.—Site of inoculation, mouse, showing cell infiltration and edema. (× 100 hematoxylin and eosin.)

Fig. 5.—Site of inoculation, guinea pig No. 227, showing cell infiltration, edema and destruction of muscle fibers. (× 100 hematoxylin and eosin.)

In the rabbits examined, the process was very intense. Hemorrhage was added to edema in the subcutaneous tissue, polymorphonuclear cells were more numerous than in the guinea pig and the destruction of

subjacent voluntary muscle fibers was considerably more extensive (Fig. 1).

MICE. No lesions were found in the gross or microscopically in the central nervous system, lung, spleen, liver, lymph nodes, intestine, pancreas, kidney, adrenal, gonads, heart or voluntary muscle.

Site of Inoculation. In the gross the subcutaneous tissue was very edematous but only slightly blood-tinged. Microscopically, there was considerable edema of the subcutaneous tissue. While the cell infiltration was of the same type as that noted in the guinea pigs and rabbits, it was less in degree in all mice examined (Fig. 4). Destruction of the voluntary muscle fibers and surrounding cell infiltration was about the same as in the guinea pigs.

In the foregoing experiments evidence has been presented that the penicillin preparations used in this investigation were toxic for guinea pigs. However, the doses given to demonstrate this toxicity have been larger, in every case, than those given to man in present clinical studies. Therefore, 3 guinea pigs (227, 228, 229) were given 1000 F.U. per kg. per day (approximately the dose given to man) in 3 subcutaneous doses daily for 20 days. During this time their weights varied, but the general trend was toward gain rather than loss. They exhibited no signs of illness except subcutaneous edema at the site of injection. On the 21st day, all pigs were killed and sections taken for study.

All inoculations had been made in the same general area, and therefore, as might be expected from the results outlined above, at autopsy the site of inoculation presented a picture of intense inflammation, both acute and chronic. Edema and fresh and older hemorrhages were frequent. There was infiltration of polymorphonuclear leukocytes and some monocytes and destruction of muscle fibers (Fig. 5). In addition, there were large numbers of fibroblasts and some fibrocytes and newly formed capillaries (Fig. 2).

In the liver of 1 out of the 3 animals, numerous foci of the type discussed above were found. .

Discussion. In the literature, reports of experiments in which animals have been given a single intravenous dose of penicillin have shown that its acute toxicity is very low. Since penicillin is not a pure substance and preparations vary in potency, the exact toxic dose has not been established. Obviously the assay of toxicity should be based on Florey units as well as milligrams of substance given. For white mice, we found the lethal intravenous dose to be about 90,000 F.U. (1 gm.) per kg. using a preparation containing 90 F.U. per mg., but in another experiment[19] using more highly purified material (500 F.U. per mg.) 250,000 F.U. per kg. caused only a slight reaction. Abraham, Chain, Fletcher, Florey, Gardner, Heatley and Jennings[1] reported the toxic dose as about 50,000 F.U. (1 gm.) per kg., but when more highly purified preparations were used, Florey and Jennings gave mice 375,000 F.U. (1 gm.) per kg. intravenously, without ill effects, and Rake et al. found that doses of 600,000 F.U. per kg. or below, were not lethal when given intravenously to mice. These results indicate that purification removes some of the substances responsible for this acute toxicity.

Very little data have been given on toxicity for other animals.[1,2,8] In our experiments 111,000 F.U. (1.2 gm.) per kg. was a lethal dose for rabbits and 75,000 F.U. (0.8 gm.) per kg. killed guinea pigs when given intravenously. In experiments reported in the literature usually no mention is made of the numbers of animals used, and in our experiments only small numbers were given any one dose because of lack of sufficient material for large scale experiments.

When penicillin was given subcutaneously over a period of several days or weeks to mice, rabbits and guinea pigs, the picture was altered. All animals showed a severe reaction at the site of injection. Edema of the subcutaneous tissue, infiltration of monocytes and polymorphonuclear leukocytes, and destruction of subjacent voluntary muscle were found in all animals, and in the rabbits and 3 of the guinea pigs there were hemorrhages. Other than this, the mice and rabbits tolerated the penicillin injections well. These results are in agreement with those of Robinson[11] who found that doses below 192,000 F.U. per kg. per day given in several subcutaneous injections daily for 5 days to mice were not toxic. In the guinea pigs, however, prolonged subcutaneous injections of penicillin prepared at different places and by different methods caused death.

Until penicillin is prepared in a chemically pure state, it will not be possible to determine whether or not contaminating substances are responsible for all of the toxicity of penicillin preparations. None of the preparations tested in these experiments were non-toxic, even a preparation having a 10-fold increase in purity was still toxic although it failed to kill all of the guinea pigs injected. It is possible that further purification will remove all of the toxic substances. However, it should be stressed that the penicillin preparations used were all as pure as, and in many cases purer than those at present in use in human treatment, and some were actually used in such treatment.

The fact that present preparations are toxic for guinea pigs when given subcutaneously does not mean that penicillin is toxic for man. When treated with the same dose of penicillin per kg. as that given to man, guinea pigs did not die and, in fact, failed to show any signs of toxicity. However, it is suggested that chronic toxicity for man be borne in mind and that care be taken to administer penicillin in several widely separated places when given subcutaneously or intramuscularly.*

Summary. 1. The acute toxicity of penicillin for mice, guinea pigs and rabbits was low; about 100,000 F.U. (1 gm.) per kg., given intravenously, caused a severe reaction and death.

2. Seven thousand to 12,000 F.U. per kg. per day of penicillin, as prepared for clinical use, given subcutaneously over a period of several days caused death of guinea pigs, but not of mice or rabbits. However,

* In his experience with the clinical use of penicillin Dr. Chester S. Keefer has found that, when given intramuscularly, penicillin dissolved in salt solution does not cause any local signs of irritation or any discomfort. When given subcutaneously and dissolved in distilled water rather than salt solution, penicillin may produce some local irritating effect, although this has not been severe enough to raise any problem. (Personal communication.)

a dose approximately that used clinically (1000 F.U. per kg.) given subcutaneously for 20 days did not kill guinea pigs.

3. All animals given penicillin subcutaneously showed a severe reaction at the site of injection.

4. Seven samples of penicillin prepared by different methods in two different places were toxic when given subcutaneously to guinea pigs for several days.

5. Large doses of sodium ascorbate did not protect guinea pigs from the toxicity of repeated subcutaneous doses of penicillin.

REFERENCES

1. ABRAHAM, E. P., CHAIN, R., FLETCHER, C. M., FLOREY, H. W., GARDNER, A D., HEATLEY, N. G., and JENNINGS, M. A.: Lancet, 241, 177, 1941.
2. CHAIN, E., FLOREY, H. W., GARDNER, A. D., HEATLEY, N. G., JENNINGS, M. A., ORR-EWING, J., and SANDERS, A. G.: Lancet, 239, 266, 1940.
3. CLUTTERBUCK, P. W., LOVELL, R., and RAISTRICK, H.: Biochem. J., 26, 1907, 1932.
4. EDDY, W.: Am. J. Pub. Health, 19, 1309, 1929.
5. FLOREY, H. W., and JENNINGS, M. A.: Brit. J. Exp. Path., 23, 120, 1942.
6. GYÖRGI, P.: Ann. Rev. Biochem., p. 309, 1942.
7. HOBBY, G. L., MEYER, K., and CHAFFEE, E.: Proc. Soc. Exp. Biol. and Med., 50, 277, 1942.
8. HOBBY, G. L., MEYER, K., and CHAFFEE, E.: Proc. Soc. Exp. Biol. and Med., 50, 285, 1942.
9. McKEE, C. M., HAMRE, D. M., and RAKE, G.: To be published.
10. RAKE, G., McKEE, C. M., HAMRE, D. M., and HOUCK, C. L.: To be published.
11. ROBINSON, H. J.: J. Pharm. and Exp. Ther., 77, 70, 1943.
12. ROSENBERG, H. R.: Chemistry and Physiology of the Vitamins, Interscience Press, p. 289, 1942.

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DISSEMINATED NECROTIZING VASCULARITIS—THE TOXIC ORIGIN OF PERIARTERITIS NODOSA

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SINCE Rokitansky[21] first described arterial aneurysms in 1852, the literature has become voluminous in regard to certain vascular problems. Kussmaul and Maier[17] in 1866 contributed a classical description of the pathology which they had noted in a patient with wide-spread vascular disease. Following the publication of this thesis the problem of vascularitis, commonly termed periarteritis nodosa, remained a closed chapter in medical annals for many years. During the past century frequent case reports with autopsies have been contributed notably those by Klotz,[12] Middleton,[13] Friedberg,[3] Harbitz,[4] Bassett and Levine,[3] Longcope,[12] Wordley,[5] Taylor and Farley,[6] Halpern and Kimball,[6] Harris,[12] Leishman,[18] and Osler.[19]

Spiegel[23] states that approximately 12% of her patients were diagnosed by clinical study during life. The purpose of this communication is to make a brief report of 10 patients, diagnosed antemortem as disseminated vascularitis, confirmed at the postmortem table, and

subsequently by microscopic study. Contrary to recently expressed opinions we have been unable to correlate these vascular lesions with preceding sulfonamide therapy.

Etiology. On reviewing the literature one is impressed with the frequency with which allergy has been alluded to as a causative factor in disseminated vascular disease. Clark and Kaplan[4] have reported 2 patients who died following intravenous antipneumococcus serum. They found widespread vascular lesions which they thought were suggestive of periarteritis nodosa. Rich[20] recently demonstrated a small group of patients whose lesions were those of widespread vascularitis which occurred subsequent to the ingestion of one of the sulfonamides, or followed administration of serum. He implied that the arterial lesions were due to an "anaphylactic type of hypersensitive reaction" and has produced similar lesions in experimental animals.

Considerable attention has been given to the possible relationship of this disease to rheumatic fever. Ophuls[18] in 1923 felt that his patients had had subacute rheumatic manifestations as a prelude to their vascular problem. Friedberg and Gross,[5] and Spiegel[22] reported a group that showed Aschoff bodies in the myocardium. However, Von Glahn and Pappenheimer[24] showed in their studies of rheumatic arteritis that the lesions were distinctly different from those seen in periarteritis nodosa. We have been unable to demonstrate Aschoff bodies in a single patient. On the other hand there were 2 instances showing involvement of the mitral or tricuspid leaflets. An infectious etiology of the disease has many adherents, notably Klotz[12] and Lamb.[14] Arkin[1] believes that the disease is a definite clinical entity probably due to a virus, but no definite virus studies have been made. We have been unable to demonstrate any infectious agent in the blood, or in the vessel walls. Gruber[6] believed that the arterial lesions were due to a peculiar hyperergic reaction resulting from a variety of infectious agents. Generalized inflammation with local necrosis has been described involving the small arteries as a residue of diphtheria, influenza, scarlet fever, typhus fever, and a variety of chronic suppurative diseases.

Visceral Lesions. The visceral lesions of vascularitis lend themselves to a ready description and classification under the microscope, but clinically diagnostic errors may be made, due to the puzzling combinations of symptoms which may present. Hematuria may suggest renal neoplasm. Abdominal complaints may lead to exploratory laparotomy. Chest symptoms are identical to those associated with pneumonia or pulmonary infarction. A better comprehension of disseminated vascularitis is obtained when a brief synthesis of these visceral lesions is made in the light of their pathologic similitude.

The Kidney. Impairment of renal functioning tissue was the most constant feature of this syndrome. All of our patients revealed widespread kidney lesions. This is comparable to Arkin's[1] group which showed an incidence of 80% renal involvement. Gruber[6] has classified these lesions as active and passive. The active lesions are the earlier ones, being initiated possibly by a hyperergic reaction on the part of

the renal vessels.   The later lesions include aneurysm, infarction, and tubular atrophy.   (Fig. 1.)   In our group there was no apparent correlation between the extent of the kidney lesion and the degree of nitrogen retention.   The character of the hypertension was not unusual except that it was a terminal affair with 3 of these patients.

The Liver and Gall Bladder.   There was hepatic involvement in every case.   Jaundice was not evident in a single instance.   There were small areas of infarction with necrosis and subcapsular hemorrhage, as well as hepatic and cholecystic thromboses with marked lymphocytic and plasma cell infiltration.   Cirrhosis of the liver was not demonstrable.

The Pancreas.   In all patients the pancreatic vessels showed lymphocytic and plasma cell infiltration with intimal thickening of the small vessels, accompanied by infarctions.
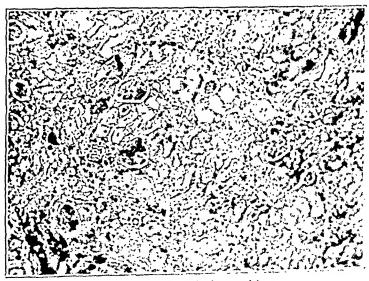
Fig. 1.—Thrombosis of several renal vessels is shown with e
(H and E stain.)   × 100.
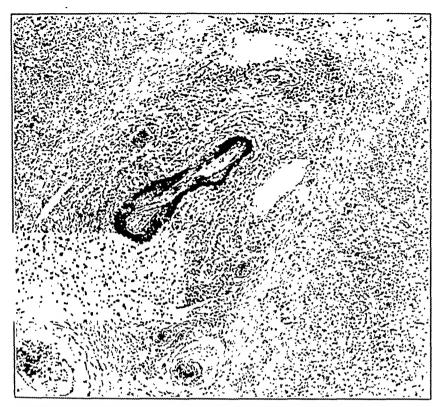
FIG. 2.—The splenic vessels show moderate intimal and medial proliferation with partial thrombosis.   (H and E stain.)   × 100.
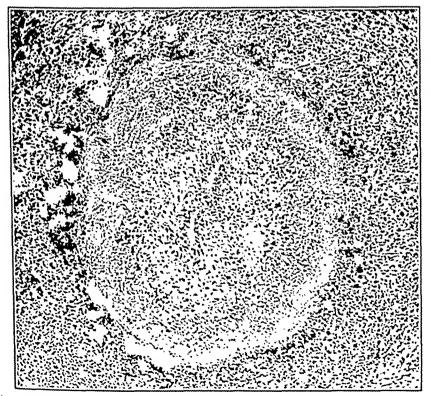
FIG. 3.—This section is from an adrenal vessel.   There is some fibrinoid change. The vessel wall reveals many plasma cells, polys, and a few lymphocytes.   (H and E stain.)   × 100.

The Gastro-intestinal Tract. Small nodules were demonstrable in the mesentery of the small bowel following the course of the mesenteric
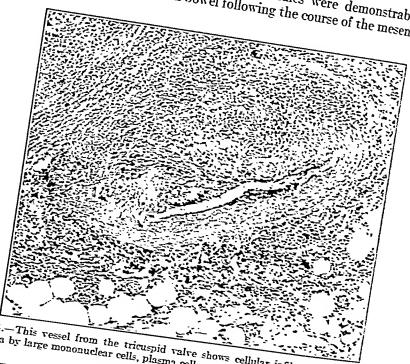
FIG. 4.—This vessel from the tricuspid valve shows cellular infiltration beneath the intima by large mononuclear cells, plasma cells, and polys. (Giemsa stain.) X 100.
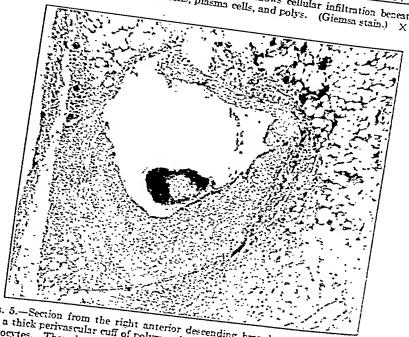
FIG. 5.—Section from the right anterior descending branch of the coronary artery shows a thick perivascular cuff of polymorphonuclear cells, monocytes, plasma cells and lymphocytes. There is marked edema of the vessel wall with a narrowing of its lumen. (H and E stain.) X 100.

veins and arteries. The appendix of 1 patient showed a localized abscess with gangrene, due to thrombosis of the appendiceal artery. Obliterative arteritis involved many of the smaller intestinal vessels, and the main gastric artery was largely occluded in 1 instance.

Cardiovascular Lesions. Involvement of the myocardium and the endocardium was frequently demonstrable. One section of a heart taken through the tricuspid valve revealed the presence of a diffuse process. (Fig. 4.) There was an area of necrosis beneath the endocardium almost perforating it in many places. These areas of necrosis were characterized by great numbers of polymorphonuclear cells, some plasma cells, and a few monocytes. The eosinophil was not prominent. The endocardial surface of the ventricle and auricle was rarely involved. One coronary artery was almost completely occluded by thrombus formation (Fig. 5). The artery wall was edematous, thickened, and

FIG. 6.—This vessel from the lung shows complete thrombosis of the vessel with early necrosis. (H and E stain.) × 100.

infiltrated by monocytes and polymorphonuclear cells. There was marked intimal hyperplasia. The muscle bundles were widely separated in a few sections with a diffuse infiltration of monocytes and plasma cells. Aschoff formation was not noted in any of these sections.

The Lung. The lung sections showed marked congestion, and the vessel walls were slightly thickened. Numerous bronchi were filled with fibrin, erythrocytes and some polymorphonuclear cells. The bronchial walls were frequently infiltrated with these cells giving evidence of bronchopneumonia (Fig. 6).

Discussion. It seems perfectly clear that the pathologic lesions herein described show marked similarity, so much so that we believe these arterial lesions point to a disease of the blood-vessels, due either to a specific bacterial agent, or a specific vascular reaction to some unidentified toxin or other harmful mechanism.

That the sulfonamides might produce these vascular lesions is

implied by Rich[20] as all of his patients had been given sulfonamide, antipneumococcus serum, or both. The lesions demonstrated so well by our sections are largely old, and it is untenable that the pathology could have developed during the acute terminal illness. Furthermore, only 4 of these patients had received sulfonamide therapy during the course of or preceding their terminal illness.

In searching for some common etiologic denominator we sought for a history of serum sickness, urticaria, and asthma. None of these conditions had played a part in the previous history of a single patient. Five had had frequent upper respiratory infections. Two soldiers had a history of rheumatic fever in early childhood. We do not know just what part these earlier infections played in the causation of this disease. The uniformity of the arterial damage has suggested a specific bacterial agent or specific vascular reaction to this agent. This idea has many early adherents, including Klotz,[12] Lamb[14] and Longcope.[16] Harris and Friedrichs[11] and Von Hann[25] were able to produce similar arterial lesions by injecting rabbits with bacterial products but these reports of experimental reproduction of the disease have not been universally accepted. Streptococci have occasionally been identified after direct culture of the arterial lesions, but our postmortem cultures of the vessels have proven to be sterile. The rich lymphatic system of the mediastinal vessels and those of the celiac axis should readily permit the entrance of infectious agents. It is thought that the bacteria enter the vessel walls through the vasa vasorum. This is demonstrated by the focal inflammatory reaction so often found in the myocardium during the course of acute rheumatic fever. This involvement of the lymphatic channels and nutrient vessels would readily damage the invaded organ.

Gruber[7] contended that periarteritis nodosa is due to a specific reaction occurring in previously sensitized vessels following the wake of a variety of infectious agents. The sensitizing infection need not be a severe one, but it may follow rheumatic fever, typhus fever, gonorrhea, furunculosis, and a variety of purulent infections. Since no bacteria were found after culture of these vascular lesions we believe that these widespread visceral lesions have a non-specific toxic origin. This view is further corroborated by Baehr,[2] who has shown early perivascular infiltration and the late stages of thrombosis with aneurysmal dilatation in the same patient.

Summary. Widespread necrotizing arteritis is herewith described in a series of autopsies. There was no history of sulfonamide sensitivity or serum sickness in these patients. Sulfonamide therapy was used in the terminal illness. The vascular lesions were widespread, and are considered to be a specific reaction of blood-vessels previously sensitized by some non-specific toxin.

REFERENCES

1. Arkin, A.: Am. J. Path., 6, 401, 1930.
2. Baehr, G.: Proc. New York Path. Soc., 19, 131, 1919.
3. Bennett, G. A., and Levine, S. A.: Am. J. Med. Sci., 177, 853, 1939.
4. Clark, E., and Kaplan, B. D.: Arch. Path., 24, 458, 1938.
5. Friedberg, C. K., and Gross, L.: Arch. Int Med., 54, 170, 1934.

6. Gruber, G.:   Zentralbl. f. Herz u. Gefasskr., **9**, 45, 1917.
7. Gruber, G.:   Virchows Arch. f. path. Anat., **258**, 441, 1925.
8. Haining, R. B., and Kimball, T. S.:   Am. J. Path., **10**, 349, 1934.
9. Harbitz, F.:   Am. J. Med. Sci., **163**, 250, 1922.
10. Harris, A. W., Lynch, G. W., and O'Hare, J. P.:   Arch. Int. Med., **63**, 1163, 1939.
11. Harris, W. H., and Friedrichs, A. V.:   J. Exp. Med., **36**, 219, 1922.
12. Klotz, O.:   J. Med. Res., **37**, 1, 1917.
13. Kussmaul, A., and Maier, R.:   Deutsch. Arch. f. klin. Med., **1**, 484, 1866.
14. Lamb, A. R.:   Arch. Int. Med., **14**, 481, 1914.
15. Leishman, A. W. D.:   Lancet, **1**, 803, 1937.
16. Longcope, W. T.:   Bull. Ayer Clin. Lab., Penna. Hosp., **5**, 1, 1908.
17. Middleton, M. S., and McCarter, J. D.:   Am. J. Med. Sci., **190**, 291, 1935.
18. Ophuls, W.:   Arch. Int. Med., **32**, 870, 1923.
19. Osler, W.:   Am. J. Med. Sci., **127**, 1, 1904.
20. Rich, A. R.:   Bull. Johns Hopkins Hosp., **71**, 123, 1942.
21. Rokitansky, K.:   Deutsch. d. k. Akad. d. Wissensch., Vienna, **4**, 49, 1852.
22. Spiegel, R.:   Arch. Int. Med., **58**, 993, 1936.
23. Taylor, J. S., and Farley, D. L.:   Bull. Ayer Clin. Lab., Penna. Hosp., **3**, 15, 1934.
24. Von Glahn, W. C., and Pappenheimer, A. M.:   Am. J. Path., **2**, 235, 1926.
25. Von Hann, F.:   Virchows Arch. f. path. Anat., **227**, 90, 1920.
26. Wordley, E. A.:   Lancet, **2**, 927, 1923.

EFFECTS OF LARGE DOSES OF A VITAMIN A CONCENTRATE IN NORMAL AND HYPERTENSIVE PATIENTS*

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Substances containing vitamin A, such as the non-saponifiable fraction of butter, have been shown to increase urea and inulin clearances in normal dogs and in dogs deprived of dietary vitamin A;[6,7] to increase the rate of glomerular filtration. Similarly, large doses of concentrates of the vitamin increased urea clearance in human beings.[8] Although the increase in inulin clearance specifies the change as one associated with increased rate of glomerular filtration, the mechanism of its increase remained unknown and it is part of the purpose of this study to determine its nature. It is also part of our purpose to examine critically the effect of large doses of a vitamin A concentrate in essential hypertension, since Govea, Peña and Villaverde[11,19] have recommended the use of the vitamin in this disease. In the first of these reports (1940) it is stated that, "of 65 cases, only 4 failed to show an impressive hypotensive effect," these being 4 cases of malignant hypertension with advanced renal lesions who, nevertheless, showed

symptomatic improvement. In their second paper (1941) it is stated that of 100 patients treated, treatment was brilliantly successful in 25%, more or less noticeably effective in 50% and of no value in 25%. In an unstated number of patients the vitamin was given intramuscularly in oil with resultant local irritation, while in others it was given orally from the start, the doses used being 100,000 to 200,000 units initially, followed by a maintenance dose of half this amount. It is unfortunate that a report which promises so much in so important a disease should, by the absence of protocols which would establish the adequacy of the observations, fail to carry conviction. While our present study was in progress, Wakerlin, Moss and Smith[20] reported on the antipressor action of preparations containing vitamin A when fed dogs with experimental renal hypertension, an observation which gives additional interest to our clinical report.

Methods. The patients studied included 2 normal females, 1, otherwise normal, suffering from obesity, 14 patients suffering from essential hypertension and 1 in whom the disease was of malignant type. All had been previously observed in this clinic for months or years, so that chance variations in the levels of blood pressure and renal function were excluded as far as possible. Further, the enthusiastic (and frequently disappointing) subjective responses of many newly observed hypertensive patients to new régimes and new physicians were obviated by continuity of observation.

Measurements of blood pressure were made weekly, bi-weekly, or, in some, daily, in the prone position after 15 to 30 minutes rest in bed. The intensity of subjective complaints (headache, dyspnea, emotional instability) was charted on an approximately standardized basis to which reference has been made elsewhere.

Renal functional changes were observed by determinations of diodrast and inulin plasma clearances and diodrast Tm's in a manner substantially identical with that of Smith, Goldring and Chasis.[14] The plasma clearances and Tm's were calculated from means of 3 collections of urine. Plasma and urine inulin were estimated by the method of Corcoran and Page.[2] Diodrast-iodine was determined by a method which, in principle, consists of oxidizing diodrast-iodine in urine or plasma filtrates with bromine water, discharging the excess bromine with sodium formate and measuring photocolorimetrically iodate-iodine in the manner described for this determination by Flox, Piteski and Alving.[4]

The changes of cardiac output were found ballistocardiographically[17] in the manner described by Taylor and Page.[18]

The vitamin A concentrate used in this study, "Alphalin" (vitamin A, Lilly) was given orally in doses ranging from 100,000 to 400,000 units of the vitamin daily for periods of from 5 to 90 days.

Results. The results of this study may be considered first with reference to the clinical effect on arterial pressure and on the course of essential hypertension and, secondly, with regard to the effects of treatment on renal and cardiac function.

With regard to arterial pressure, treatment with vitamin A did not alter the mean blood pressure level or its range of variation in either normotensive or hypertensive subjects (Table 1). The treatment did not result in any change in the complaints of those of the hypertensive patients presenting symptoms of their condition, nor, on the other hand, in any untoward effect.

Table 1.—Effect on Arterial Pressure of Treatment With Vitamin A Concentrate

| Patient | | Diagnosis | Months prior obs. | Dosage (thous. U.) | Days treated | Before treatment | | | After treatment | | |
No.	Initial					Lowest	Highest	Average	Lowest	Highest	Average
1	E. W.	Norm.	2	200	14	100/70	128/82	120/78	104/76	126/85	122/80
2	J. S.	Norm.	2	400	28	98/64	110/77	108/76	100/62	114/80	106/72
3	L. B.	Obese	6	100	14	110/70	120/90	120/80	108/68	124/88	118/80
4	J. B.	Ess. HT	24	100	28	182/114	220/150	180/124	176/116	190/126	184/123
5	G. B.	Ess. HT	18	100	14	200/120	240/142	214/130	220/136	220/150	220/143
6	H. B.	Ess. HT	72	200	5	160/100	220/130	198/114	178/96	224/128	194/112
7	R. G.	Ess. HT	37	400	18	156/90	184/116	172/98	180/100	206/120	182/110
8	S. H.	Ess. HT	60	200	39	190/102	244/124	210/114	190/106	220/120	208/112
9	V. L.	Ess. HT	72	200	41	182/100	220/108	194/106	180/90	204/110	190/100
10	L. P.	Ess. HT	15	200	57	158/98	200/114	179/112	156/96	184/118	174/110
11	P. R.	Ess. HT	6	200	25	158/104	194/124	172/114	158/96	200/120	172/110
12	N. S.	Ess. HT	5	400	28	166/90	240/140	226/120	166/94	250/122	224/122
13	C. T.	Ess. HT	85	200	80	140/80	186/110	170/94	142/76	184/100	172/90
14	E. T.	Ess. HT	80	200	90	190/100	266/154	218/122	198/90	246/128	228/126
15	N. Y.	Ess. HT	36	100	24	140/114	190/140	178/128	154/120	192/136	177/130
16	M. N.	Mal. HT	15	200	28	180/114	220/150	210/130	206/106	250/148	208/140
								For group 178/109			For group 180/110

No. = case number; Initial = patient's initials; Norm. = normal; Ess. HT = essential hypertension; Mal. HT = malignant hypertension. Months prior obs. indicates the number of months during which the patient's blood pressure had been observed.

The effects on renal function were at once less consistent and more interesting than those on arterial pressure. The results of individual observations are tabulated in Table 2 and the net effects summarized in relation to dosage and duration of treatment in Table 3. Of 2 normotensive patients (Nos. 2 and 3) 1 (No. 2) showed a modest increase in plasma diodrast clearance during treatment. In the 1 patient (No. 16) suffering from malignant hypertension, secretory tubular mass (Tm_D) had decreased after 13 days of treatment without corresponding changes in the clearances of diodrast and inulin. On the 28th day of treatment of this patient renal function had greatly deteriorated and the disease progressed inexorably to death in uremia.

TABLE 2.—EFFECT ON RENAL FUNCTION OF TREATMENT WITH VITAMIN A CONCENTRATE

Patient No.	Day before during or after treatment	Dose (thous. units)	Clearance (cc. per 1.73 sq. m./min.)		Filtration fraction	Tm_D (mg. diodrast iodine per 1.73 sq. m./min.)	Total protein (gm./100 cc.)	Hemat. (%)	B.P. (mm. Hg)
			Diodrast	Inulin					
2	0 B	0	747	139	0.18	51 0	8 0	34	92
	28 D	400	857	148	0.17	53 0	8.4	38	97
	32 A	0	626	140	0 22			38	90
3	0 B	0	715	137	0 19	58 0	6 3	38	105
	14 D	100	663	140	0.21	..		43	105
4	0 B	0	344	107	0.31	39 4	6 8	45	161
	14 D	100	444	107	0.24	..	.	49	158
	110 A	0	384	123	0 36			50	153
5	0 B	0	366	95	0 26	37 0	6 6	39	161
	14 D	100	638	168	0.26	..	..	42	178
	90 A	0	589	123	0 21	..	..	36	157
6	0 B	0	..	..	.	21 9	7.3	40	154
	5 D	200	344	95	0 28	22 4	7.2	40	150
	5 A	0	299	84	0.28	..	..	41	153
7	18 D	400	831	192	0.23	51 3	7 1	39	145
	28 A	0	702	163	0 23	57 6	..	41	155
	48 A	0	550	183	0.33	42 9		37	156
8	0 B	0	364	102	0.28	37 0	6 7	44	179
	39 D	200	497	108	0 22			47	164
9	0 B	0	462	95	0.21	40 8	6 4	44	168
	12 D	200	426	84	0.20	43 0	.	41	156
	38 D	200	636	112	0 18		.	39	140
	15 A	0	534	132	0.25			39	135
10	0 B	0	474	87	0.18	31 7	7 1	39	125
	50 D	200	589	129	0.22	42 9	7 0	41	131
	21 A	0	525	121	0.24	52 3	8.3	43	151
11	0 B	0	590	145	0.25	46 8	6 1	38	140
	25 D	200	604	144	0 24			38	141
12	0 B	0	456	111	0.24			38	155
	28 D	400	483	129	0.27	52 0+	.	37	128
	20 A	0	436	98	0.22	49 0	6 9	40	156
13	0 B	0	624	137	0 22	55.0	7 0	41	122
	6 D	200	694	130	0.19	53 6	7 1	40	129
	31 D	200	660	141	0 22	51 0+		50	134
	30 A	0	671	183	0 27	65 5	7 1	39	136
	44 A	0	695	165	0.24	51 4	7 0	37	134
14	0 B	0	354	63	0 18			44	134
	0 B	0	321	59	0 18	23 9	6 0	45	134
	16 D	200	606	124	0 20	44 7	5 4	47	152
	33 D	200	565	120	0 21			45	159
	49 D	200	679	115	0 17	46 5	5 5	40	167
	50 A	0	668	107	0 16	43 1		38	157
16	0 B	0	137	50	0 39	16 2	6 1	45	175
	13 D	200	143	54	0.35	13 4	6 1	43	159
	28 D	200	88	17	0.20			48	152

Patient No. as in Table 1. Day of treatment indicated as 0 = control, B = before, D = during, A = after treatment with vitamin A. Tm_D = Secretory tubular mass. Clearances and Tm_D corrected to body surface area of 1.73 sq. m. per minute. Clearances in cc. per minute of plasma clearance and Tm_D in mg. diodrast iodine (D–I) per minute. Total protein = plasma total protein, gm. per 100 cc. Hemat. = hematocrit index in per cent. B.P. = blood pressure on the day of observation in mm. Hg mean of systolic and diastolic pressure.

TABLE 3.—SUMMARY OF EFFECTS OF TREATMENT WITH VITAMIN A ON RENAL FUNCTION AND CARDIAC OUTPUT AS RELATED TO DOSAGE AND DURATION OF TREATMENT

			Percentile changes from control				
Patient No.	Day of observation	Total dose U. × 10⁵	Clearance		Filtration fraction	Tm_D	Cardiac output
			Diodrast	Inulin			
6	5 D	10	+19	+13	0	0	+18
13	6 D	12	+11	−15	−16	0	+ 3
5	14 D	14	+74	+77	0	—	—
3	14 D	14	0	0	0	—	—
9	12 D	24	0	0	..0	0	− 9
16	13 D	26	0	0	0	−16	+10
4	14 D	28	+29	0	−23	—	—
14	16 D	32	+90	+110	+10	+85	+18
11	25 D	50	0	0	0	—	—
13	31 D	62	0	0	0	(+20)	—
14	33 D	66	+70	+104	+16	—	
7	18 D	72	+51	0	−31	+29	+14
9	38 D	76	+39	+18	−15	—	—
8	39 D	78	+36	0	−20	—	—
14	49 D	98	+110	+96	0	+95	—
10	50 D	100	+24	+48	+20	+35	+ 8
2	28 D	112	+15	0	0	0	+12
12	28 D	112	0	+15	+12	0	—

Patient numbers and observation as in Tables 1 and 2. Accumulated total dosage of vitamin in 100,000's of units. The changes of diodrast and inulin clearances, filtration fraction, Tm_D, cardiac output (C.O.) and hematocrit index are recorded as percentile differences from control or (Patient 7) post-treatment levels. Differences of less than 10% in clearances or Tm_D were considered negligible in the tabulation. A dash (—) indicates that no observation was made. The bracketed ( ) observation of Tm_D in patient No. 13 was made 30 days after discontinuing treatment.

Among the 10 patients suffering from essential hypertension, all but 1 (No. 11) showed at one time or another increased clearances or tubular secretory mass. Diodrast clearance increased in 8, inulin clearance in 6 and tubular secretory mass (Tm_D) in 4 of 7 patients in whom observations were made. Because the increase in inulin clearance (rate of glomerular filtration) did not parallel the increase in plasma diodrast clearance (effective renal plasma flow), filtration fraction (ratio of inulin/diodrast plasma clearance) was unchanged in 3, increased in 2 and decreased in 5 patients. It is noteworthy that in 3 patients (Nos. 7, 10 and 13) the maximum increase in Tm_D was observed after treatment with vitamin A had been discontinued respectively for 28, 21 and 30 days.

Cardiac output as measured by the ballistocardiograph was determined in 1 normotensive (No. 2) and 7 hypertensive subjects before and during treatment. Cardiac output increased in the normotensive during treatment in association with an increase of plasma diodrast and inulin clearances of less than 10%. Among the hypertensives, cardiac output was unchanged in 1 (No. 13), although effective renal plasma flow had increased somewhat at the time of observation; in 6 other hypertensives, it was decreased in 1 (No. 9) in whom clearances had not changed and was increased in 5. In 4 of these 5 the increased cardiac output was associated with increased renal plasma flow as measured by plasma diodrast clearance. The increase of cardiac out-

put without increased renal plasma flow was recorded in the patient (No. 16) suffering from malignant hypertension and here note should be taken that the increased cardiac output was associated with maintenance of renal plasma flow and filtration rate at control levels in spite of decreasing renal tubular secretory mass (Tm_D), i. e., there had developed a relative increase in blood flow to residual functioning tissue. In all 6 subjects whose cardiac outputs increased during treatment, the increase was due to tachycardia and was not accompanied by increased stroke volume.

Discussion. Although the presumed antipressor effects of preparations containing vitamin A were attributed to the action of the vitamin,[11,19] studies on the antipressor action of the vitamin in renal hypertensive dogs[20] have indicated that the effect is not one of the vitamin as such, since it does not develop after administration of the pro-vitamin, carotene, but rather persists after destruction of the vitamin A by irradiation. Harrison, Grollman and Williams[5] and Grollman and Harrison[5] have observed antipressor action of fish-oil concentrates in renal hypertensive rats which persists and may even be increased after destruction of the vitamin with CrO_3 or by irradiation. They have also demonstrated the antipressor ineffectiveness of the pro-vitamin (carotene) or of highly purified natural vitamin A concentrates. It therefore appears likely that whatever antipressor action preparations of the vitamin may have in renal hypertension in animals is due to some substance associated with the vitamin in the materials administered and not to the vitamin itself.

Our failure to observe antipressor effect in carefully studied cases of essential hypertension during the administration of large doses of the vitamin may be attributed to (a) the absence of the supposed antipressor substance which may accompany vitamin A in some concentrates and not in others; (b) some possible difference in the mechanism of experimental renal hypertension in animals and essential hypertension in man; (c) administration of insufficient quantities of the antipressor material or (d) accidental selection of refractory patients. However, considering these several possibilities, we note (a) to our best information the preparation of vitamin A used was of a type which should contain all that is present in many commercial preparations of the vitamin; (b) although their identity is not established, there are at least weighty analogies which link essential hypertension in human beings with experimental renal hypertension in animals; (c) the dose of the vitamin given by Wakerlin, Moss and Smith[20] was some 5 to 15 times greater than we have used in terms of unitage per kilo of body weight; (d) with 1 exception (No. 16) the patients suffered from rather mild and labile essential hypertension and should have shown improvement should such be possible with this method of treatment. It is therefore possible that our negative results as regards the effect of vitamin A on blood pressure may be due to the use of amounts too small to reveal effects observed in experimental hypertension with larger doses, although the amounts used were approximately equal to those given by Govea, Peña and Villaverde.[11,19] The use of much

larger doses and for longer periods would be almost prohibitively expensive in clinical practice. Nevertheless, we are continuing this aspect of the study.

The renal functional changes, viz., increased renal blood flow, glomerular filtration rate and tubular secretory capacity for diodrast are of special interest. As this study was in progress, we were kindly informed that similar renal effects were under observation in normal dogs fed vitamin A concentrates.[1] The increased glomerular filtration rate observed by Herrin and Nicholes[7,8] is therefore evidently due to increased renal blood flow, although the cause of the renal hyperemia is still not apparent. Filtration fraction, which measures the relative level of intraglomerular pressure, is slightly more often decreased than not during treatment, which suggests that the increased renal blood flow is in part the result of efferent arteriolar vasodilation. But, since dilation of efferent arterioles at constant levels of arterial pressure and afferent resistance would result in increased blood flow without any change in filtration rate, it appears that with efferent vasodilation there developed a like change in the glomerular afferent arterioles, a view supported by calculation of our data according to the methods suggested by Lamport.[10] The fact that the vitamin preparation causes renal vasodilation suggests that this property, if it affects arterioles throughout the body, may be responsible for the antipressor effects observed experimentally in dogs and rats.

The increase in tubular capacity for diodrast secretion (Tm_D) was observed in patients treated with large doses and over long periods. In 3 of these it seems to have reached its peak after the vitamin had been discontinued and, in the 2 cases (Nos. 7 and 10) who had shown increased renal flow, after renal hyperemia had subsided. The increase in secretory capacity may represent either (a) an increase in the "concentration" of the hypothetical carrier substance responsible for transport of diodrast through the renal tubular cells or (b) an increase in cell mass. There is no evidence at hand to decide which factor prevails in this instance. The renotropic action of steroid hormones (reviewed editorially[9]) might bear on this decision were it not[21] that the increased secretory capacity provoked in dogs by administration of large doses of testosterone is not associated with concurrent changes in the rates either of renal plasma flow or of glomerular filtration, but is apparently due to local hypertrophy of the cells of the convoluted tubules.[12,13] The renotropic action of the steroid thus contrasts with that of the vitamin A preparation and the suggestion is made that the effect we observed may be the result of prolonged hyperemia rather than a trophic action of the vitamin or some concomitant substance.

The renal vasodilation which developed in most of our patients was not itself sufficient to cause a decrease in the level of arterial pressure, possibly because of the simultaneous increase in cardiac output. It is noteworthy that the increase in cardiac output under treatment with vitamin A is wholly the result of tachycardia, and thus resembles the effect of fever rather than the reduction of peripheral resistance occasioned in hypertensives by treatment with antipressor renal

extracts.[18] The action of the vitamin was not associated with increased oxygen consumption in 2 cases observed by Herrin and Nicholes.[8] Rather it appears that the cardiac action of the vitamin is a response to local renal vasodilation.

Even in patient No. 16 (13th day of treatment) whose renal tubular mass decreased by 18% as the result of nephrosclerosis, concurrently the residual tubular mass was perfused by an increased volume of blood. The increase in cardiac output was thus again associated with renal vasodilation although effective renal blood flow had not increased.

With regard finally to possible therapeutic use of preparations of the vitamin, the factor of cost of the large doses necessary to excite a renal response combines with its variable effectiveness to suggest that further study is necessary before it or some derivative or concomitant present in the preparation can be recommended. A similar variation in effect was noted by Herrin and Nicholes[8] and found *not* to be correlated to the plasma levels of vitamin A. With reference to hypertension, the absence of antipressor effect in subjects who showed improvements in renal excretory function is not surprising, since it is our view that the pressor and excretory aspects of renal function are distinct and, in large measure, independent.[3] The results do indicate that large doses of vitamin A may have therapeutic value in states of renal insufficiency and degeneration not primarily due to essential hypertension, as, for instance, in Bright's disease. This aspect of its use is now under study.

Summary. Administration of doses of a preparation of vitamin A in amounts ranging from 100,000 to 400,000 units daily for from 5 to 90 days in 3 normotensive and 14 hypertensive patients did not alter the levels of arterial pressure. Observations of renal function in 2 normotensive and 11 hypertensive patients revealed increased effective renal blood flow in 9, increased glomerular filtration rate in 7 and increased tubular secretory capacity for diodrast (Tm_D) in 4 of 7 hypertensive patients in whom this function was tested. The increase in effective renal blood flow was usually associated with increased cardiac output, the result of tachycardia and not of increased stroke volume.

Conclusions. 1. Vitamin A concentrate is ineffective in the treatment of essential hypertension in doses of 100,000 to 400,000 units daily for from 5 to 90 days.

2. The vitamin concentrate causes renal vasodilation and increased functional capacity for secretion of diodrast with increased cardiac output. The suggestion is made that it may have application in the treatment of degenerative renal diseases.

REFERENCES

1. BING, R. J., and SMITH, H. W.: Personal communication, 1942.
2. CORCORAN, A. C., and PAGE, I. H.: J. Biol. Chem., 127, 601, 1939.
3. CORCORAN, A. C., and PAGE, I. H.: J. Lab. and Clin. Med., 26, 1713, 1941.
4. FLOX, J., PITESKY, I., and ALVING, A.: J. Biol. Chem., 142, 147, 1942.
5. (a) HARRISON, T. R., GROLLMAN, A., WILLIAMS, J. R., JR.: Ms. Personal communication, 1942. (b) GROLLMAN, A., and HARRISON, T. R.: Proc. Soc. Exper. Biol. and Med., 52, 162, 1943.
6. HERRIN, R. C., RABIN, A., and FEINSTEIN, R. N.: Am. J. Physiol., 119, 87, 1937.
7. HERRIN, R. C., and NICHOLES, H. J.: Am. J. Physiol., 125, 786, 1939.

8. HERRIN, R. C., and NICHOLES, H. J.:   J. Clin. Invest., **19**, 489, 1940.

9. J. Clin. Endocrin., Editoriàl, **3**, 111, 1943.

10. LAMPORT, H.:   J. Clin. Invest., **20**, 535, 1941.

11. PEÑA, J. GOVEA, and VILLAVERDE, M.:   Riv. Cubana de. cardiol., **2**, No. 5, 332, 1940.

12. SELYE, H.:   J. Urol., **42**, 637, 1939.

13. SELYE, H.:   J. Urol., **46**, 110, 1941.

14. SMITH, H. W., GOLDRING, W., CHASIS, H.:   J. Clin. Invest., **17**, 263, 1938.

15. SMITH, H. W.:   Studies on the Physiology of the Kidney, Porter Lectures, Univ. of Kansas, Lawrence, 1939.

16. SMITH, H. W.:   J. Clin. Invest., **20**, 631, 1941.

17. STARR, I., RAWSON, A. J., SHROEDER, H. A., and JOSEPH, N. R.:   Am. J. Physiol., **127**, 1, 1939.

18. TAYLOR, R. D., and PAGE, I. H.:   AM. J. MED. SCI., **205**, 66, 1943.

19. VILLAVERDE, M., and PEÑA, J. GOVEA.:   Boletin de la Assn. med. de Puerto Rico, **33**, 238, 1941.

20. WAKERLIN, G. E., MOSS, W. G., and SMITH, E. L.:   Proc. Centr. Soc. Clin. Res., **15**, 30, 1942.

21. WELSH, C. A., ROSENTHAL, A., DUNCAN, M. T., and TAYLOR, H. C.:   Am. J. Physiol., **137**, 338, 1942.

Since this manuscript was submitted a complete report by Wakerlin and Moss (Proc. Soc. Exp. Biol. and Med., **53**, 149, 1943) has emphasized the point of view that antipressor activity is characteristic of some, but not all, vitamin A concentrates tested in renal hypertensive dogs. The details of the procedure used to determine diodrast iodine will appear shortly in the Jour. Lab. and Clin. Med.

PROGRESS

OF

MEDICAL SCIENCE

THERAPEUTICS

THE MEDICAL USE OF THIOCYANATES IN THE TREATMENT OF ARTERIAL HYPERTENSION*

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Review of Earlier Work. Although Claude Bernard[12] in 1857, made the first report on the pharmacologic actions of thiocyanate by demonstrating its depressant action on the animal heart, up to 1926 the majority of the experimental work on the medical use of thiocyanate was carried out in Germany.

In that country, Edinger[25b] in 1900, as quoted by Nichols,[61] treated satisfactorily a number of hypertensive patients with thiocyanate. Three years later, Pauli[65] got pleasing results in arteriosclerosis and hypertension, and Westphal and Blum[82] (1926) reported favorable results in another large series of hypertensive patients.

This last report stimulated investigators outside of Germany, among the most important of whom was Barker,[9] who in 1936 utilized the method of Schreiber[73] to measure the blood thiocyanate of patients under thiocyanate therapy. He found that the blood level was the important criterion for effective therapeutic dosage and for the prevention of toxicity. In 1941, Griffith et al.[37] described a micro method for determining blood thiocyanate levels, which considerably simplified the situation and he also suggested criteria for the selection of suitable patients.[38]

The Pharmacologic Actions of Thiocyanate Related to Its Use in Arterial Hypertension

A. Pharmacodynamic Actions. 1. ON THE CENTRAL NERVOUS SYSTEM. *Sedation.* Bernard[12] suggested and found a sedative action by thiocyanate. Pauli[65] confirmed this and went on to try the drug on hypertensive and

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* Submitted as a third-year paper in Pathology, University of Pennsylvania Medical School, December, 1942.

nervous patients.   Smith[75] classed it as a mild hypnotic and sedative.
Symptoms varying from drowsiness and weakness to psychoses are re-
ported.[11,13,38,42,54,71,79]   However, there is little mention of this soporific
action in the most recent literature.   Goodman[35] ignores it completely
and Nichols[61] could find none, although he expressively looked for it.
Fineberg[28] also found none.   In paradox, Bancroft[7] suggests thiocyanate
to counteract the narcotics, due to its ability to prevent the precipitation
of protein.   .   ..

Irritation of the Anterior Horn Cell.   Wald *et al.*[79] reported that dogs
dying from thiocyanate poisoning went into hyperirritative states, as in
strychnine poisoning.   They assumed this to be a result of anterior horn
cell irritation.   Nichols[61] confirmed their statement that the pre-death
stage was one of increased motor excitability.   However, Jahr[43] injected
thiocyanate into a dog's 4th ventricle without causing hyperirritability.

2. ON THE MUSCLE.   *Paralytic Action.*   Bernard[12] compared thiocyan-
ate to curare in its effect on muscle.   It paralyzed a frog's leg, but the
contralateral reflex was not lost.   The drug must be injected intramuscu-
larly or cutaneously for this effect.   Setschenow[74] noted the same paralytic
effect, but claimed a skin anesthesia came first.   Weakness is one of the
commonest toxic symptoms of thiocyanate overdosage,[29] but whether
this is from actual paresis or a subjective reaction is a matter of question.
Jahr[43] found the fatigability of a rabbit's tibialis was increased when
perfused with thiocyanate.   He quotes Taubman and Heilborn[76b] as finding
the same result in isolated muscle.   Westphal[82] reported that there was
no relaxation of arterial muscle if it was immersed in thiocyanate solution.
Adrenalin would still cause a contraction in the muscle in the solution.

Stimulation of Smooth Muscle.   Kotte[45] quotes Ellinger as finding
increased tone in isolated arterial strips immersed in thiocyanate solution.

3. ON BLOOD AND VASCULAR ORGANS.   *Decreased Viscosity.*   Doles[25a]
reports that patients with macrocytosis have a decrease in cell volume
after treatment with thiocyanate.   The total serum protein has been
found decreased.[11]   The albumin globulin ratio has been reduced by
thiocyanate.[82]

Vasodilation.   Goodman[35] gives a relaxation of smooth muscle as one of
the effects of thiocyanate.   Griffith[38] believes the drug releases a spasm
of the arterioles, because it will often increase the cutaneous lymphatic
flow, and because the best effects in the treatment of arterial hypertension
are obtained in patients whose arteries are without organic change.
Bernard[12] said thiocyanate would increase the diameter of a vessel in a frog's
mesentery.   Westphal[82] confirmed these findings.

However, Robinson[69] could find no evidence of peripheral dilation in
the arteries or arterioles.   Kotte[45] with Karl Smith found no vasodilation
by perfusing thiocyanate through an isolated rabbit's ear.   I also found
no increase in the peripheral blood flow of cats as measured by the
themostrohmur, the blood thiocyanate level being gradually raised until
death ensued.

Hypotensive Effect.   Since the first suggestion of its use to treat hyper-
tension by Pauli,[65] this effect of thiocyanate has been in question.   Gold-
blatt[33] found that a toxic level was needed to produce a blood pressure fall
in hypertensive dogs.   Grollman *et al.*[39] found no significant blood pressure
fall in rats, with oral dosage.   Barker and Davis[10] demonstrated that
sympathectomy sensitized the patient to thiocyanate, so that a small dose
would create the same hypotensive effect after operation that a large one
would, prior to operation.   Kurtz[45] confirmed this.   Hamilton[41] found no

significant drop in blood pressure in dogs treated with thiocyanate. Nowhere in the literature could I find a mention of a hypotensive action in a laboratory animal, except when it was quite toxic. Quattlebaum[66] took 9 gr. q.d. for 1 week and there was no change in the blood pressure, except for a transient 10 mm. drop in systolic pressure on the 7th day. The author makes no mention of any subjective symptoms.

However, the majority of clinical authors believe there is a definite hypotensive effect in a large percentage of cases of arterial hypertension. This will be discussed later.

Hypertensive Effect. Lodholz[48] found a blood pressure increase terminating in death, in dogs fatally poisoned with thiocyanate. Setschenow[74] had also found this action. I found the same phenomena in dogs and cats prior to exitus from thiocyanate.

Cardiac Depression. Bernard[12] noted that the heart was depressed and stopped beating when he injected frogs and rabbits with thiocyanate. The cessation was in diastole, but he was unable to determine whether this was a result of muscular weakness or lack of excitation. Paschkis[64a] reported that heart block was caused by the drug in frogs, and would be relieved by atropine. Nichols[61] says it depresses the normal heart.

However, Massie[52] reports that there is no change in the EKG with thiocyanate. Starr[76] says the cardiac output in a good many conditions that he studied often actually increases as the blood pressure goes down. Several authors have actually found a decrease in heart size upon dosage with the drug.[11,46,54]

Depression of the Blood Cholesterol. Askanzy[2] has said that thiocyanate decreased the blood cholesterol. Lodholz[48] quotes Monk in saying that the liver is the storehouse for thiocyanate. He blames the decreased cholesterol on liver function depression.

Respiratory Stimulation. Paschkis,[64a] as quoted by Nichols,[61] reported a respiratory increase with thiocyanate; Jahr[43] denied this. I found a similar effect in cats, upon the intra-arterial injection of sodium thiocyanate. However, I found the same effect after the injection of sodium chloride solution. Thus I attributed the stimulus to a non-specific irritation of peripheral nerve endings in the limb. Comroe[20] injected the region of the carotid body and found no respiratory changes.

4. ON GLANDS. *Mucus Glands.* Goodman[35] described the action of thiocyanate as increasing the mucus flow, in the manner of iodine. Pauli[65] said it would lead to a rhinitis. Mayer[54] reported rhinorrhea in patients treated with the drug; Takacs[76a] said it increased the stomach secretion.

Endocrine Glands. Wald et al.[79] found in their patients, after treatment with the drug, that a goiter occurred that improved with iodine. Barker[9,11] found thyroid enlargement and facial myxedema in some of his patients while under treatment. Pauli[65] said thiocyanate was harmful on top of thyroid dysfunction. He also stated that thiocyanate does not pass through the body without affecting the endocrines. Kobacher[44] presented 1 case in which symptoms of thyroid dysfunction were produced by the drug, and relieved by its omission. The woman's hearing was depressed during the existence of the thyroid lesion, but returned following cessation of the drug. Webster says "a cyanide" is the factor leading to the production of the experimental "cabbage goiter." Fahlund[27] reported a case of painful enlargement of the thyroid in less than a week of thiocyanate treatment. He believed it was an instance of sensitivity.

Healy[42] tested the adrenals of thiocyanate dosed rabbits and found a high concentration of the drug in that organ.

5. On the Kidneys. *Diuretic Action.* Westphal[82] reported 3 cases with increased renal function in spite of decreased blood pressure. Nichols[61] found a diuretic action in rabbits. Healy[42] noted a diuresis and thiocyanate-uria in rabbits. Barker[11] found diuresis as a toxic symptom. Jahr,[43] however, found renal damage in rabbits resulting from the drug.

6. On the Liver. *Depression of Liver Metabolism.* Major[51] reported a decrease in the blood guanadine bases. Damage to the liver and bone marrow as seen in benzene poisoning has been found.[11] Robinson[69] found the metabolism of the liver decreased as much as 40%, as measured in the Warburg apparatus, with a thiocyanate. concentration of 20 mg. per 100 cc.

B. **Toxic Actions of Thiocyanate.** 1. On Patients. There appear to be toxic effects directly from the action of the drug, and secondarily, from the decreased blood pressure. They will be taken up in that order.

Direct Effects of Moderate Severity, With Low Blood Levels. A blood concentration of 12 mg. per 100 cc. or less is regarded as low. Doles[25a] gives the basis for this classification. Weakness and fatigue are reported in this concentration range.[2,11,31,38,53,54,69,79] Doles[25a] says these symptoms will often go away spontaneously at the end of 2 to 6 weeks of therapy. A dermatitis of the erythematous type, with or without pruritus.[13,69,71] is sometimes seen. Also a maculopapular eruption of the seborrheic areas of the chest and back.[65] Gager[31] and Kurtz[46] reported dermatologic lesions of the face and corners of the eyes and mouth. Somnolence has been reported,[9,75,79] but is usually in the higher concentration group. Nausea is reported.[13,54,64] Griffith[38] says nausea can be reduced by diluting the solution. Mayer[54] used enteric coated capsules.

Direct Effects of Greater Severity With Greater Than Therapeutic Blood Levels. Gastric hemorrhage was noted by Nerking;[60] Franz also found this. Vintilesco[78a] is quoted as saying that his fatal case had gastric necrosis at autopsy. Purpura has been reported;[59,69] also a decrease in libido;[31,69] nervousness;[9,38,64] and bloody diarrhea.[13]

Mental symptoms are prominent in this group. Hallucinations,[42,69] slurring speech, unsteady gait and disorientation[11] have been recorded. Mandibular neuritis, with a questionable relation to thiocyanate, has been reported.[13]

A severe complication of thiocyanate treatment is exfoliative dermatitis, which clears up, if at all, rather slowly after cessation of medication. Alopecia often accompanies it. Cases of exfoliative dermatitis have been reported by numerous authors.[5,61,69,78,80] Pyrosis, anorexia and nausea are an index of high or increasing thiocyanate level.[79]

Sensitivity to Thiocyanate. Fahlund[27] describes a case of acute "thyroiditis," which he ascribes to sensitivity to thiocyanate. Thiocyanate sensitivity may be responsible for many of the toxic symptoms, for the tolerance varies greatly from person to person. Griffith[36] finds a small percentage of persons who exhibit a toxic reaction to their first small dose of thiocyanate and attributes this to a sensitivity.

Indirect Toxic Effects of Thiocyanate Due to the Fall in Blood Pressure. An anginal attack in an elderly patient without any previous history of angina has been reported[69] during thiocyanate treatment. The same author also reports another patient with increase in anginal attacks after thiocyanate. Other reports of anginal pain during thiocyanate therapy exist.[46,64]

In discussion of these cases in relation to the thiocyanate treatment of hypertension, several points should be made. First, Barker[9] has shown that the drug should not be used without knowing the blood level. In

only 2 of these cases was the blood level known; therefore, the remainder should be discarded in a strict consideration of its toxic effects. It is obvious that the first 3 cases do not reflect discredit on the medicinal use of thiocyanates   Second, Hamburger's case was not reported as a true death from thiocyanate, the drug being postulated only as contributory.

TABLE 1.—SUMMARY OF RECORDED FATALITIES

Reporter	Sex	Age	Date	General
Lesser (see Russell[71])	M	5S	189S	Suicide
Kobert (see Russell[71])	F	..	1906	5 gm. of drug
Vintilesco and Popesco[75a]	M	27	..	100 gm.
Healy[42]	F	63	..	5 gr. t.i.d.
Goldring and Chasis[34]	F	40	1932	10 gr. per day
Ibid[34]	F	56	1932	12 gr. per day
Saleeby[72]	..	..	1931	Died after acute respiratory inf.
Garvin[32]	F	71	1941	Blood level 18.7
Hamburger[40]	M	..	1941	30 gr. in 7 days; was in hypertensive encephalopathy
Russell[71]	M	52	1942	Blood concentration greater than 21 mg. per 100 cc.; urea clearance 27%

In both of the cases where the blood level was known, it was high. Barker[9] recommends an 8 to 12 mg. per 100 cc. level, certainly no higher than 15 mg. per 100 cc.   The last case also had a low urea clearance. In spite of this, these 2 cases clearly died from the effects of thiocyanate.

Experimental Work on Thiocyanate Toxicity.   The potassium salt is 5 times as toxic as the sodium salt when injected intravenously in animals; but there is no difference per oris.[1]   However, Westphal[82] said the potassium salt is more potent as a hypotensor, even when given per oris.   This has not been confirmed,[71] but rather repudiated by the indiscriminate use of either salt without noticeable difference.   There were no uniform lesions found in dogs poisoned with thiocyanate.[2]   Laufer postulated that the hyperirritability found in poisoned dogs might result from hypocalcemia. However, Jahr[43] produced convulsions even when calcium was injected along with the thiocyanate.   Healy[42] put forward the idea that all the toxic symptoms might be from hypo-adrenemia, as he noted a concentration of the drug in that organ.   Griffith[38] attributes the dermatitis and diarrhea to idiosyncrasy.   Fineberg[28] found some gastric irritation from thiocyanate.   Jahr[43] produced weight loss in dogs, cats and porpoises with the drug.   He regarded this as a result of gastric mucosal irritation, producing diarrhea.   The drug caused albuminuria and hematuria in rabbits. Diarrhea, central nervous (spinal cord) irritability, spastic paresis, opisthotonus, cramps, and death are the progressive symptoms of fatal thiocyanate poisoning in animals.   Thiocyanate does not convert to cyanide in the body.[75]   However, Nerking[60] says prussic acid can be produced in the mouth from caries, sodium chloride and thiocyanate.

The Clinical Use of Thiocyanate in the Treatment of Arterial Hypertension and Results

A. The Clinical Use.   *Dosage.*   Before Barker's[9] report on the necessity of determining the blood level of the drug, many empirical dosage methods were advised.   In the light of our present knowledge, the actual dose is not as important as the blood level.   Goodman[35] recommends a 0.3 gm. (5 gr.) dose per day.   Griffith[36] recommends a 0.2 to 0.4 gm. dose per day initially and a blood thiocyanate level taken by at least the end

of the first week. The following doses should be entirely regulated by the blood level. The micro method of Griffith[37] is the most practical for frequent thiocyanate blood level determinations. The blood level of 15 mg. per 100 cc. should never be exceeded. Barker[9] recommends a level between 5 to 6 mg. per 100 cc. at first. If there is no benefit, raise it to between 8 and 12 mg. per 100 cc. Blood thiocyanate levels of 40 to 60 mg. per 100 cc. without untoward symptoms have been observed.[18]

Route. No mention of any other route than oral for the routine treatment of hypertension with thiocyanate was found in the literature. Freeman[30] recommends enteric coated capsules to prevent gastric upsets. Griffith[38] reports that diluting has decreased gastric irritation in his experience.

The Salt Used. There has been no confirmed evidence in the literature of the advantage of one salt over the other. Sodium thiocyanate and potassium thiocyanate are used almost equally in the reported cases.

Tolerance. No tolerance has been noted.[19] No other mention of tolerance was found in the literature.

Latent Period. No beneficial effects from the drug appear for at least a week. The effects may last 2 months after the drug is stopped.[15] The drug may be retained until about the 6th day.[23] Dogs retain toxic effects for around 2 weeks.[33]

Distribution of the Drug in Body Fluids. Thiocyanate is not evenly distributed to all parts of the body, but does reach an equilibrium with the body fluids in about 2 hours.[23] It is not, however, distributed to the cerebrospinal fluid.[45]

Indications and Contraindications. Griffith advises the use of thiocyanate only in selected cases[38] of hypertension with some degree of capillary mobility or reducible spasm. This is in contrast with the general opinion, which seems to be that one should use thiocyanate in any hypertensive individual unless it is contraindicated.

Kidney, heart damage, cardiac decompensation, and general inflammatory conditions have been given as contraindications.[49] Acute nephritis and renal insufficiency are proposed.[19] As a general principle, patients with renal retention and poor clearance are more liable to radical toxic effects, either from increased blood concentrations, or damage to the kidney *per se*.[11,82] However, Kurtz[46] says that chronic nephritis is no contraindication, and other authors[52,56] say albuminuria is no contraindication. Toxic symptoms are more frequent in advanced age[42] and some workers advise that a patient who is more than 60 should not take the drug.[52,56,69] A good heart and relatively normal BUN are a necessity.[52] Thiocyanate will have a harmful effect in toxemia of pregnancy.[19] Patients with advanced arteriosclerosis do not respond well to the drug.[8,14,69] Logefeil[49] gives a complete list of contraindications including all hypertensive states except essential arterial hypertension without sclerosis. He contraindicates the drug in inflammations of the upper respiratory tract, as it will cause further irritation. The drug is recommended as a preoperative medication for sympathectomy.[21]

B. **Results From the Use of Thiocyanate in the Treatment of Hypertension.** *Results in the Pre-Barker Epoch.* The majority of authors writing prior to 1936[2,14,15,28,31,33,49,50,53,56,62,63,65,72,75,82] were in favor of the use of thiocyanate in hypertension. Some[3,4,5,34,57,64,67,81] regarded the drug as too toxic, and one thought there was little or no specific hypotensive action.[3]

In general, the authors who found good results, got a drop of systolic blood pressure of 30 to 40 mm. of mercury and a diastolic drop of 10 to

15 mm. of mercury or more. They were satisfied that the toxic manifestations, if they did occur, were justified by the results obtained.

The Post-Barker Epoch. The majority of the authors are still in favor of the use of thiocyanate, by a greater margin than before 1936[8,9,11,13,16,18,22,24,25a,29,37,38,45,46,52,54,55,66,68,69,77,79] The greater part by far of this group regulated the drug dosage by watching the blood level. Some reporters still feel the treatment is not worth the danger.[6,25,26,32,33]

Goldblatt[33] is doubtful of the existence of the hypotensive effect, as it has never been demonstrated in a laboratory animal without marked toxicity. None of the clinical reports have completely eliminated all the variables which might cause unrelated blood pressure variation. Robinson[70] reports normal blood pressure variation in the region of 10 mm. per week at 120 mm. and it is even greater at higher pressures. It would be difficult to design an experiment which would take such an order of variation into account.

Theories of the Hypotensive Action of Thiocyanate in the Hypertensive Patient

A. **Decreased Cardiac Output.** *Through Cardiac Depression.* Bernard[12] said he found depression of the animal heart from thiocyanate. In my animal experiments, the heart action was not depressed until immediately before death. Thiocyanate has been contraindicated in cardiac failure,[75] but no note has been found in the literature of cardiac failure being produced or intensified by the drug. The electrocardiogram shows no changes after thiocyanate administration.[53]

Through the Endocrines. An effect through the endocrine system has been suggested by Healy[42] who found increased thiocyanate in the adrenals after drug dosage. He postulates hypoadrenemia leading to a blood pressure fall. Hypothyroidism[9,11] might result in the blood pressure drop.

Through Decreased Venous Return. The muscular paralysis reported by Bernard[12] would lead to this effect.

B. **Decreased Peripheral Resistance.** *Through Vasodilation.* This has been discussed under the pharmacodynamic actions of thiocyanate. Westphal[82] expresses the general opinion of the German authors, that the blood cholesterol was increased in the majority of their hypertensive patients, and that they employed thiocyanate to decrease it. According to their theory, the sterol decreases the permeability of the smooth muscle cell wall, leading to constriction of the arteriolar vessels. The drug would counteract this, by decreasing the cholesterol concentration.

Through Decreased Blood Viscosity. Doles[25a] reported a decrease in erythrocyte volume of macrocytic patients with essential hypertension when they were given thiocyanate. Similarly, Jahr[43] stated that thiocyanate did not decrease the red blood cell count, but did decrease the hemoglobin content. Taubman,[76b] however, says that thiocyanate did decrease the blood count in his experience.

A decreased blood protein, or altered alb/glob ratio would change the serum viscosity.[82] There is also the possibility that the cohesion of the cells in the blood might be varied.

Through Removing Calcium Deposits. Pauli[65] thought he was removing calcium from the arteriosclerotic vessel walls with the drug. Leroy[47] used thiocyanates to dissolve cataracts with the same thought in mind.

C. **Decreased Blood Volume.** Jahr[43] suggested that a shift in the water balance *via* the endocrines might be the basic cause of some of the

good and bad effects of thiocyanate. No other mention in the literature of a change that could be related to blood volume was found.

D. Miscellaneous. Meakins[57] suggests that an effect on tissue oxidation might cause the hypotension. A depression of liver metabolism has been mentioned before.[69] A decrease in the guanidine bases has been found with thiocyanate treatment,[51] and has been suggested as the basis of the blood pressure fall.[75] Edinger put forward the increase in nitrogen and sulphur excretion as the cause. The rationale is obscure.

In general, sex, age, retinal lesions, urinary findings, myocardial damage, orthodiagram, cytologic findings and serology show no relation to the hypotensive effect.[15,58] It should be noted that actually some of the subjective effects for which thiocyanate is given also appear to be caused by it.

Conclusions as to the Use of Thiocyanate in the Treatment of Hypertension

The majority of clinical workers believes that thiocyanate has a definite hypotensive effect in the arterial hypertensive patient. However, this hypotensive effect has not been demonstrated in the laboratory. The mechanism by which this clinical blood pressure drop occurs is not known. It is to be hoped that a complete statistical analysis will be done in the future to prove this suspected hypotensive effect.

A satisfactory method for the administration of thiocyanate has been suggested by Barker[9] which will give minimal toxicity if handled correctly. Thiocyanate should never be given without blood levels being taken. Thiocyanate is not a blanket cure-all for "hypertension" and should be used only in selected cases and where no contraindication exists.

Any relief of subjective symptoms bears minimal relation to the blood pressure drop.[2,3,13,68]

REFERENCES

(1.) Anderson, R. C., and Chen, K. K.: J. Am. Pharm. Assn. Sc. Ed., 29, 152, 1940. (2.) Askanzy, S.: München. med. Wchnschr., 74, 1793, 1927. (3.) Ayman, D.: J. Am. Med. Assn., 95, 246, 1930. (4.) Ayman, D.: J. Am. Med. Assn., 96, 1852, 1931. (5.) Ayman, D.: J. Am. Med. Assn., 93, 1671, 1929.

(6.) Baker, T. W., and Brunsting, L.: J. Am. Med. Assn., 108, 549, 1937. (7.) Bancroft, W. D., and Richter, G. H.: J. Phys. Chem., 35, 215, 1931. (8.) Barker, M. H.: Wisconsin Med. J., 36, 28, 1937. (9.) Barker, M. H.: J. Am. Med. Assn., 106, 762, 1936. (10.) Barker, M. H., and Davis, L.: Ann. Surg., 110, 1016, 1939. (11.) Barker, M. H., Lindberg, M., and Wald, H.: J. Am. Med. Assn., 117, 1591, 1941. (12.) Bernard, C.: Leçons sur les Effets des Substances Toxique et Medicamentes, p. 395, 1857. (13.) Blaney, L. F., Geiger, A. J., and Ernst, C. R.: Yale J. Biol. and Med., 13, 493, 1941. (14.) Bolatin, M. T.: Illinois Med. J., 62, 557, 1932. (15.) Borg, J. F.: Minnesota Med., 13, 293, 1930. (16.) Bynum, W. T.: J. Oklahoma State Med. Assn., 32, 444, 1939.

(17.) Cannady, E. W., and Allen, H. N.: Illinois Med. J., 82, 146, 1942. (18.) Caviness, V. S., Umphlet, T. L., and Royster, C. L.: J. Am. Med. Sc., 204, 688, 1942. (19.) Chasis, H., and Goldring, W.: New York State Med. J., 31, 1322, 1931. (20.) Comroe, J.: Personal communication. (21.) Corcoran, A. C., and Page, I. H.: Arch. Surg., 42, 1072, 1941. (22.) Covey, G. W.: Nebraska State Med. J., 25, 363, 1940. (23.) Crandall, L. A., and Anderson, M.: Am. J. Digest. and Nutr., 1, 126, 1934. (24.) Crockett, K. A., and Moendi, L. G.: J. Am. Med. Assn., 120, 982, 1942. (25.) Current Comment: J. Am. Med. Assn., 114, 2391, 1940. (25a.) Doles, H. M.: South. Med. J., 31, 1225, 1938 and 32, 299, 1939.

(25b.) Edinger, A., and Treupel, G.: München. med. Wchnschr., 47, 717, 767, 1900. (Quoted by Nichols, J. B.) (26.) Egloff, W. C., Joyt, L. H., and O'Hare, J. P.: J. Am. Med. Assn., 96, 1941, 1931.

(27.) Fahlund, G. T. R.: Proc. Staff Meet. Mayo Clinic, 17, 289, 1942. (28.) Fineberg, M. H.: J. Am. Med. Assn., 29, 1823, 1930. (29.) Flexner, M.: South. Med. J., 34, 917, 1941. (30.) Freeman, I.: Bull. School Med. Univ. of Maryland, 26, 109, 1941. (31.) Gager, L. T.: J. Am. Med. Assn., 90, 82, 1928. (32.) Garvin, C. F.: J. Am. Med. Assn., 112, 1125, 1939. (33.) Goldblatt, H., Kahn, J. R., and Lewis, H. A.: J.

Am. Med. Assn., 119, 1193, 1942. (34.) Goldring, W., and Chasis, H.: Int. Med., 49, 311, 1932. (35.) Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941. (36.) Griffith, J. Q., Jr.: Personal communication. (37.) Griffith, J. Q., Jr., and Lindauer, M. A.: Am. Heart J., 14, 710, 1937. (38.) Griffith, J. Q., Jr., Lindauer, M. A., Roberts, E., and Rutherford, R. B.: Am. Heart J., 21, 94, 1941. (39.) Grollman, A., Harrison, T. R., and Williams, J. R.: J. Pharm. Exp. Ther., 69, 76, 1940.

(40.) Hamburger, W. W.: Med. Clin. North America, 25, 1929, 1941. (41.) Hamilton, W. F., Pund, E. R., Slaughter, R. F., Simpson, W. A., Jr., Colson, G. W., Coleman, H. N., and Bateman, W. H.: Am. J. Phys., 128, 233, 1940. (42.) Healy, J. C.: New England Med. J., 205, 581, 1931.

(43.) Jahr., E. G.: Arch. f. exper. Path. u. Pharm., 169, 429, 1932.

(44.) Kobacher, J. L.: Ohio State Med. J., 38, 431, 1942. (45.) Kotte, H.: Ohio State Med. J., 39, 20, 1943. (46.) Kurtz, C. M., Shapiro, H. H., and Mills, C. S.: Am. J. Med. Sc., 202, 378, 1941.

(47.) Leroy, B. L.: New York Med. J., 90, 802, 1909. (48.) Lodholz, E.: Univ. Pennsylvania Med. Bull., 18, 279, 1905. (49.) Logefeil, R. C.: Minnesota Med., 12, 150, 1929. (50.) Lörcher, W.: Deutsch. med. Wchnschr., 53, 23, 1927.

(51.) Major, R.: Am. J. Med. Sc., 176, 637, 1928. (52.) Massie, E.: Internat. Clin., 3, 198, 1941. (53.) Massie, E., Ethridge, C. B., and O'Hare, J. P.: New England J. Med., 219, 736, 1938. (54.) Mayer, M., and Reisinger, J. A.: Med. Bull. Vet. Admin., 19, 42, 1942. (55.) Reference omitted. (56.) McNeill, J. F.: Psychiatric. Quart., 7, 254, 1933. (57.) Meakins, J., and Scriver, W.: Canad. Med. J., 25, 285, 1931. (58.) Moia, B., and Quesada, R.: Rev. argent. de cardiol., 9, 41, 1942. (59.) Mosenthal, H. O.: J. Am. Med. Assn., 114, 1548, 1940.

(60.) Nerking, J.: Deutsch. med. Wchnschr., 39, 945, 1913. (61.) Nichols, J. B.: Am. J. Med. Sc., 170, 735, 1925.

(62.) Palmer, R. S.: Am. J. Med. Sc., 184, 473, 1932. (63.) Palmer, R. S., Silver, L. S., White, P. D., Bloomberg, W., and Hahn, R. G.: New England Med. J., 201, 709, 1929. (64.) Palmer, R. S., and Sprague, H. B.: Med. Clin. North America, 13, 215, 1929. (64a.) Paschkis, H.: Med. Jahrb., p. 531, 1885. (Quoted by Nichols, J. B.) (65.) Pauli, W.: München. med. Wchnschr., 4, 153, 1903.

(66.) Quattlebaum, J. T.: J. South Carolina Med. Assn., 38, 112, 1942. (67.) Queries and Minor Notes: J. Am. Med. Assn., 102, 637, 1934.

(68.) Ritter, W. L.: J. Missouri Med. Assn., 38, 238, 1941. (69.) Robinson, R. W., and O'Hare, J. P.: New England J. Med., 221, 964, 1939. (70.) Robinson, S. C., and Brucer, M.: Arch. Int. Med., 64, 409, 1939. (71.) Russell, W. O., and Stahl, W. C.: J. Am. Med. Assn., 119, 1177, 1942.

(72.) Saleeby, P. J.: New Orleans Med. and Surg. J., 83, 93, 1931. (73.) Schreiber, H.: Biochem. Ztschr., 163, 241, 1925. (74.) Setschenow: Virchow's Arch. f. Path. Anat. u. Physiol. u. f. klin. Med., 14, 356, 1858. (75.) Smith, A. G., and Rudolph, R. D.: Canad. Med. J., 19, 288, 1928. (76.) Starr, I.: Personal communication.

(76a.) Takacs, L.: Ztschr. f. d. ges. exper. med., 50, 432, 1926. (76b.) Taubmann, G, and Heilborn, R.: Arch. f. Exp. Path. u. Pharm. 152, 250, 1930.

(77.) Tuckwiller, P. A.: West Virginia Med. J., 38, 235, 1942. (78.) Tyrrel, J. D.: Canad. Med. J., 22, 80, 1930.

(78a.) Vintilesco, J., and Popesco, A.: Ann. d'hyg. pub., 25, 239, 1916. (Quoted by Russell, O., and Stahl, W. C.)

(79.) Wald, M. E., Lindberg, M. A., and Barker, M. H.: J. Am. Med. Assn., 112, 1120, 1939. (80.) Weis, C. R., and Ruedemann, R.: J. Am. Med. Assn., 93, 988, 1929. (81.) Weiss, S.: Med. Clin. North America, 19, 343, 1936. (82.) Westphal, K., and Blum, R.: München. med. Wchnschr., 73, 1187, 1926.

VITAMIN E AND ITS RELATION TO REPRODUCTION*

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In 1923 Evans[10] first announced a dietary constituent that was necessary for normal reproduction in rats. He at that time showed that without this constituent male rats were infertile due to damaged epithelium, and females failed to carry their young to term. Since then we have advanced

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* Submitted as a report in the third year course in Pathology in the University of Pennsylvania School of Medicine, December, 1942.

far in our knowledge of this substance; it has been taken apart, synthesized, and various deficiency diseases have been produced in animals which were then cured with this substance. Yet we know very little about its actual workings in the human body. The attempt is made here to assemble salient features which have come to light during these past 20 years from study of this substance, which is called vitamin E.

Space forbids reviewing the entire field at this time, hence this paper must be limited to the part played by vitamin E in relation to reproduction. Its rôle in the muscular dystrophies, amyotrophic lateral sclerosis, malignancy, and so forth, must be entirely omitted. For a brief review of these aspects see Mason.[58a]

The active principle of vitamin E has been thought to be associated with anti-oxidants since Olcott and Mattill[69–72,75] first showed the substance present in lettuce oil. Later, Bradway[17] showed that it is present in tomatoes, carrots, and wheat germ oil and is accompanied by inhibitors which prolong the induction period of auto-oxidizable fats.

Vitamin E has been shown to be a durohydroquinone.[43,61] Evans[41,42] prepared from the unsaponifiable portion of wheat germ oil a fertility potent factor which is known as alpha tocopherol, a reduced polycylic compound of the sterol type. He produced an alpha and a gamma fraction from cottonseed oil; only the alpha fraction is obtained from lettuce.

Other studies[12,14,29,31,35,43,47,61,71,73,95,97–99,104] on the biologic aspects of the chemistry of vitamin E will not be considered here, suffice to say that: (1) Absorption spectrum analysis shows a band at 2940 Ångstroms[54,71] which is not connected with the activity of the vitamin.[29,66,70,71,73] (2) It is stable to light and heat. (3) It is destroyed by bromination, ozone, perbenzoic acid, potassium amide, and so forth.[72,112] (4) Concentrates cannot be hydrogenated. (5) Alpha tocopherol (a 6-hydroxy chroman) has been synthesized.[95,97]

Bioassay. Vitamin E may be assayed by keeping adult female rats on an E deficient diet and noting the ability to bear living young following administration of varying amounts of concentrates by mouth. Bacharach[14] showed that failure to mate, failure to ovulate or failure to implant was not related to the amount of vitamin E present. He suggests[13] that biologic activity of a sample of vitamin E should be taken to mean its content of tocopherol, not its effect on vitamin E deficient rats.

Palmer,[79] using single oral doses, found that the correlation between live litter efficiency and placental implant was significant. At best, however, the assay is qualitative. He found a high retention of vitamin E in processed wheat germ oil kept 1 year at room temperature in sealed cans.

Makenzie[51] recommends the use of rabbits in estimating the content of vitamin E necessary to cure muscular dystrophy. Emmerie[37] described a colorimetric method of identifying and assaying tocopherols. Mason[56] has proposed assay by the uterine index method, which is the weight of uterine contents in grams plus the number of viable fetuses at term divided by 5. Mason[58c] in a new and rapid method to bioassay vitamin E bases his values on the number of live fetuses and the weight of uterine contents at the 16th day of pregnancy. The presence of 2 or more viable fetuses in utero at the 16th day of life affords criteria of positive response equal to, and in certain cases more reliable than, that based on delivery of progeny at term. He states that there are other advantages to be gained from this shorter test period in the bioassay, namely the economy in animal care and diet, and the information gained by examining the uterus as to atypical states, and positive responses.

It has been recommended by the members of the International Vitamins Standardization Conference that synthetic racemic alpha tocopherol acetate shall be adopted as the International Standard for vitamin E.[45] The International Unit has been defined as the vitamin E activity of 1 mg. of the Standard Preparation. This is the average quantity which prevents resorption of gestation in rats deprived of vitamin E when the substance is administered orally. The strength of the Standard Solution is such that 1 gm. contains 10 International Units (or 10 mg. of alpha tocopherol acetate). The standard has certain physical and chemical properties which are described in the literature.[45b]

Relation to Other Biologic Products. Adamstone[7] has shown the relation of vitamin E to anthracene and its derivatives. He believes that it is just as necessary for the normal utilization of anthracene substances as vitamin D is for calcium and phosphorus.

CHOLESTEROL, an anthracene substance, disappears from the brains of young chicks along with degeneration of the brain when these chicks are kept on vitamin E free diets. In muscular dystrophies due to vitamin E deficiency, the cholesterol content increases. Vogt-Møller[110] has reported hypocholesteremia in pregnant women subject to habitual abortions.

CALCIFEROL, also an anthracene substance, when used in the form of cod-liver oil to supplement a vitamin E free diet, produces a lymphoblastoma, whereas halibut oil produces an erythrophagocytosis.

ANDROGEN, the anthracene substance from the testes, needs vitamin E for normal utilization, as shown by Adamstone[4] using caponized fowl.

PITUITARY GONADOTROPIN and vitamin E play different rôles. Vezar[104] showed an abundance of vitamin E had a stimulating action on the sexual cycle. He can induce precocious maturity in young females but requires the presence of ovaries. Vitamin E cannot be substituted for in vitamin E free diets by estrin, progesterone, or anterior pituitary extract. Most evidence favors vitamin E as essential for the normal functioning of the anterior lobe of the pituitary. Changes in the pituitary gland will be discussed under Pathology.

Moore[65] showed that vitamin E deficiency also decreased the reserves of vitamin A. Shute[93a] has shown that neuritis in pregnant women due to vitamin B deficiency was $2\frac{1}{2}$ times more frequent when associated with a vitamin E deficiency.

Physiology and Pathology. *Production of Vitamin E Free Diets.* There are several methods which can be used, namely: (*a*) By adding cod-liver oil, butter fat, or lard to the diet; *i. e.*, oxidation by fatty substances.[9–57] (*b*) By treating the diet with ferric chloride; this produces sterility in 12 weeks in rats.[113] All the germinal epithelium is lost, and all the fetuses in the first gestation are resorbed. (*c*) Drying is a necessary factor for inactivating vitamin E. (*d*) Possible destruction of vitamin E by other fats in diet was suggested by Mattill.[59]

Relation to Growth and Development. Martin[54] says that vitamin E increases early growth. However, Olcott and Mattill[74] concluded that the improvement in early growth was not due to vitamin E.

That vitamin E may be a factor in the hatchability of chick eggs was shown by Adamstone,[5] because fertile eggs produced by pullets fed on vitamin E deficient ration failed to hatch a normal amount of healthy chicks. Embryos from eggs on a vitamin E free diet usually died by the 4th day of incubation. The pathologic conditions causing death were: (*a*) degeneration of the circulatory system; (*b*) hemorrhages and groups of histocytes; (*c*) a lethal ring in the blastoderm which surrounds the embryo

and causes death by starvation, asphyxia, and general toxemia. Barnum[16] showed that adding 15% wheat germ oil to the diet gave normal eggs.

Cunningham and Hopkirk[22] found that diets high in protein or low in protein produced good growth but induced sterility by damaging male germinal epithelium resembling vitamin E deficiency. Vezar[108] showed that normal rats started their estrous cycles at an average body weight of 100 gm., but vitamin E deficient rats began their cycles at weights averaging 30 gm. Emerson[36] says there is a response to wheat germ oil after a plateau in weight has been reached. The growth stimulating factor is in the non-saponifiable portion. Olcott[77] says that rats on a vitamin E free diet grew as fast as those on high vitamin E diets, and supported the claim that early growth is not due to vitamin E. Goettsch[44a] reared 7 generations of mice on vitamin E low diets and found no retardation in growth.

Hormone Balance. Nelson[68] showed that the male hypophysis from vitamin E deficient rats was more potent in the gonad stimulating hormone than from normal rats, but less potent than from glands of castrates. Others[82] have shown that anterior pituitary extract or pregnancy urine do not prevent resorption of embryos in vitamin E deficient females and that pituitary deficiency is not the primary cause of resorption. After castration the basophil cells of the anterior pituitary are altered and the gonadotrophic potency of whole gland increases. This is in disagreement with Nelson.[68]

Singer[94] says the thyroid is hypoplastic and Underhill[106] confirmed this finding in vitamin E deficiency. The latter also described changes in the anterior lobe of the pituitary; namely, the acidophils are small and degenerate and have pyknotic nuclei and the cytoplasm stains poorly. Also there is a degeneration of the basophils with a decrease in gonadotropin. No evidence of histologic changes and no castration cells have been found in pituitaries of vitamin E deficient females, as have been claimed for the males. The thyroid of male rats kept on vitamin E deficient diets for periods of 6 to 15 months showed more histologic activity and weighed more grossly than normal controls of the same age and sex. An increase in the BMR was found also. However, these effects were found to be due to deficient iodine content in the water rather than the lack of vitamin E, for by increasing the iodine in the diet to normal, the thyroids became normal and the BMR returned to normal.[16a]

Effect on Female Reproductive System. It was Evans[40] who first pointed out the "resorption" of the fetus in pregnant female rats kept on certain diets, which we now know to be lacking in vitamin E. Since then, many have reported the effect of vitamin E in increasing the number and viability of the litter. Evans,[40] however, in a review of the literature, states that large amounts of vitamin E do not improve reproduction beyond normal limits, and that large amounts during the first gestation will protect a second, even though on vitamin E free diets, but not a third gestation.

Its necessity for the embryonic growth in animals other than the rat and mouse is being established; for example, Vogt-Møller[110] injected 20 cc. of sterilized wheat germ oil into cows which had repeatedly failed to become pregnant and as a result 33 out of 50 cows so injected became pregnant. Schioppa[83a] found large doses of wheat germ oil increased litter size, and in the diet of sows, the mortality of suckling pigs was reduced.

Subcutaneous injections of vitamin E have no effect on the ovaries, uterus, the opening of the vagina or cornification of the vagina in imma-

ture female rats.[71] Urner[107] found intra-uterine changes, namely, a gross purplish discoloration and congestion of normal pregnancy. After the 12th day, no normal uterus and no embryos were found. Histology remained normal until the 10th day. Moore[64] found a brown discoloration with pigment in the muscle cells.

In rats, injection of estrogens or anterior pituitary extract will not substitute for vitamin E in deficient diets. Szabo[103] showed that vitamin E caused uterine hypertrophy in pseudopregnant mice but not in normal mice. Histologically this hypertrophy is seen to be due to an increase in connective tissue and muscle fibers. McCullagh[62] and Marchesi[53] observed no histologic changes in ovaries of vitamin E deficient females and also there was no direct effect on the vagina, the non-gravid uterus, nor on fertilization and gestation; however, the pregnancy was terminated by resorption of the fetus.

Effect on Lactation. Evans[39] says other factors are necessary for lactation beside vitamin E. Sure[102] attempted to prove that vitamin E is made up of two fractions, one for fertility and one for lactation, but concluded that no specific vitamin was essential for lactation. In mothers depleted of the reserve of lactation promoting substance, the young responded to wheat germ oil.

Mason[56,53] showed that a transfer of vitamin E occurs across the placental barrier. Concentration of vitamin E in the placenta and the uterus of high vitamin E mothers is 5 times that of a full-term fetus.[56,57] On stock diets made deficient in vitamin E, he showed that degeneration of the testes of rats should occur in the same length of time, but that if the young were suckled by high vitamin E mothers, a delay in the degeneration of the testes from 20 to 40 days indicated that mammary transfer had occurred.

In humans, Shute[92] showed an increased output of milk in 35% of cases where lactation was poor upon adding wheat germ oil to diet. Sixty per cent were able to nurse longer than 3 months.

Effect on Male Reproductive System. Vitamin E deprivation in male animals brings about a response which differs from that in the female, in that the changes occurring in the male are irreversible; that is, they are not alleviated or relieved by administration of wheat germ oil or by other sources of vitamin E. This has been explained by the fact that in the male the damage is to the animal's own tissues, in contrast to the female, where the damage is to the fetal tissue.

Male fowl on vitamin E free diets for 1 year showed normal fertility of sperm.[9] By the end of the 2d year, 2 males were sterile. Sperm smear showed that structural changes occurred shortly after the commencement of the experiment. One showed testicular atrophy, and 3 showed degenerative changes. Mature sperm degenerate first and gradually degeneration proceeds to the outside of the seminiferous tubules.

Mason[56] and Marchesi[53] showed that diets deficient in vitamin E, but adequate in the other vitamins, have produced definite histologic injury to rat testes. Deficiency in vitamin A has produced testes degeneration not influenced by vitamin E. The histologic changes due to vitamin E deficiency in male testes are: (*a*) chromolysis and fusion of mature spermatozoa; (*b*) removal through the rete testis to the epididymis; (*c*) nuclear change and liquefaction of spermatids and secondary spermatocytes, and segregation of chromatin to form a crescent. Abnormal cells fuse into multinucleate masses; (*d*) Sertoli tissue shows no degenerative change though the nuclei have been irregular and syncytium more fibrous. Kudr-

jaschow[48a] says that the Sertoli nuclei exhibit structural changes which he thinks are related to disturbance of nutritive function. It takes roughly 50 days for the degeneration process to reach completion. There was no evidence produced to show regenerative capacity on the part of the seminiferous tubules. Forty gm. of lettuce a day had no curative effect. Other findings in male organs were discoloration of the seminal vesicles and decrease in weight of the testes and the prostate.

DiBassi[28a] examined human testes from 165 patients dying of sudden death. Of these, 44 showed multinucleate giant cells derived from spermatids, histologically similar to the picture of vitamin E deficient rat testis. Also on milk diets, male rats became sterile and showed the same histologic picture. However, females on the same diet produced living young, so changes in germinal epithelium cannot be attributable solely to vitamin E deficiency.[111]

A loss of interest in the female fowl by the male was noticed by one observer.[44] Others have claimed that these changes in sex behavior were not due to loss of vitamin E because they were not reversible when vitamin E was provided in the diets. Adamstone[9] says that the loss of sex interest on the part of the male fowl appears before any marked degeneration of the testis and before secondary sex characters show regression.

Distribution in Body Tissues. Cuthbertson[26] showed that vitamin E was stored in adipose tissue only when diet was unusually high in it. No storage took place in any other tissue. Moore[64,65] showed spectroscopically that it was only deposited in depot fat. Mason[58c] has assayed the vitamin E in the tissues of 338 rats which received either 4, 100, or 10,000 times the minimal daily requirement of vitamin E. He found that on the low intake the heart, lungs, and spleen contained almost twice as much vitamin E per gram of fresh tissue as the musculature, body fat and other vital organs; the liver had the least. On moderate intake of vitamin E, storage is augmented in the viscera, musculature and fat. The heart, lungs and spleen receive most of it. The liver's supply of vitamin E is increased 14 times, while the mammary gland concentrates twice as much as the liver. At the excessively high levels of vitamin E intake, the liver has about 150 times the amount which it contains at lower levels, hence it is the most valuable guide to previous intake and storage. Only a small fraction of the total amount of vitamin E ingested is stored in the rat, which confirms the suggestion that tocopherols may not be effectively absorbed from the gut or are readily broken down in the body.

Theoretical Concepts of Mode of Action of Vitamin E. Since no one has produced evidence as to how vitamin E acts in the body, but little space will be given to theories. Adamstone[10] believes that normal cell division requires vitamin E and in vitamin E deficiency abnormal excessive division occurs. The first recorded speculation was that vitamin E played a rôle in the utilization of iron. This was exploded and rejected by Mattill.[59] Vogt-Møller[110] has called it a morphogenic hormone. Drummond and Underhill[29] think its fundamental rôle is in hormone balance. Adamstone[7] has already pointed out its relationship to anthracene substances. Shute[92] has the idea, that in humans at least, vitamin E holds estrogens in equilibrium during pregnancy, and that a vitamin E deficiency results in an excess of estrogen in the blood. Some think[44,54,55] that vitamin E consists of two fractions, already mentioned. Wright and Drummond[115] suggest that tocopherols are part of the enzyme oxido-reduction system in the body. Ridgeway[80] showed, however, that no oxidation products of alpha tocopherols are likely to take part in reversible oxidations in the body.

Clinical Considerations. INDICATIONS FOR USE. Definite proof for the value of vitamin E as a remedy for human sterility is manifestly difficult to secure. Many causes are associated with human sterility and, as we have pointed out, animal experiments indicated vitamin E is concerned with only one phase of the female reproductive process, namely, the blood supply and nutrition of the embryo; and in the male with the maintenance of testicular function. By analogy, an inadequate diet of vitamin E in the human male might be revealed by non-viability or even complete absence of sperm; in the female, by abortion—the physiologic counterpart of absorption in rats. Such analogies, however, are dangerous as they may imply too much or too little. All we can do is to point out certain facts where vitamin E has been used in treating pathologic conditions and the manner that is recommended for such use.

Habitual Abortion. Chances of a full-term pregnancy in untreated cases of habitual abortion are about 60% after 2 successive abortions and about 27% after 3; while after 4 abortions only 6% can hope to have a full-term delivery.[15] Shute[85] suggests this condition is caused by an excess of anti-proteolytic activity which damages the nutrition of the trophoblast.

Currie[23-25] reported 30 cases of habitual abortion in which 18 were carried to term, 3 to more than the 34th week, and 5 were carried over 5 months, all on wheat germ oil. In a second series of known habitual aborters, 23 out of 29 delivered at term and the remaining 6 were carried over 6 months, again on wheat germ oil.

Vogt-Møller[109] reported 20 cases in which no anatomic or physiologic abnormalities could explain the repeated abortions; 17 of these bore living children after treatment with wheat germ oil. In a second series of 52 cases of habitual abortion, 38 living young were born following treatment with wheat germ oil. He first tried wheat germ oil in sterile cows and next in 2 human subjects who had aborted 4 and 5 times respectively. These 2 women had normal term pregnancies.

Watson[113] and Tew[113a] reported success in a series of 34 out of 46 cases of habitual abortion, but no benefit was obtained in overcoming cases of sterility.

Shute[85] says that in the blood serum of aborting women, a deficiency of vitamin E has permitted estrogenic substance to acquire a dominant position. Resistance to proteolysis disappears when treated with vitamin E. Further, he has shown that the blood serum of rats on vitamin E free diets developed the ability to resist tryptic ferment, comparable to the blood serum of aborting women.[87] Oral administration of wheat germ oil overcame this resistance. He reported 72% success in treating habitual abortion by vitamin E.[87]

Threatened Abortion. Another indication for vitamin E therapy is in the treatment of threatened abortion. Silbernagel and Burt[27] have recently reported a series of 140 cases treated in this manner. Their criteria for diagnosis was vaginal bleeding with or without crampy pains. They made comparative tests with various methods of therapy which included conservative measures of bed rest and sedation; progesterone; alpha tocopherol acetate alone, given intramuscularly; alpha tocopherol acetate intramuscularly and orally; alpha tocopherol acetate intramuscularly and natural tocopherol given orally; alpha tocopherol acetate orally only; and natural tocopherols orally alone. Their results indicate that alpha tocopherol acetate hypodermically plus natural tocopherols orally is the ideal regimen for treating threatened abortion, having 85% of their women go to term without losing the fetus. Oral natural tocopherol alone

and oral wheat germ oil alone gave good results in 42% and 33% respectively. Progesterone alone carried only 18% of the cases to term and alpha tocopherol acetate intramuscularly carried 20% through.

Senile Vaginitis. Shute[93] has reported success in using wheat germ oil to treat this condition, especially associated with excess of estrin and hypothyroidism.

Abruptio Placentæ. This lesion, in which the placenta separates prematurely, is said to occur in about 0.3% to 2.8% of pregnancies. Many cases are undoubtedly overlooked because the early symptoms are not recognized. The condition in the advanced stage resembles shock, with or without uterine bleeding. Uterine pain, rigidity and tenderness, and sacral backache are characteristic. The patient may die of hemorrhage or may abort a macerated fetus. Shute[85] showed that 78% of these patients had a deficiency in vitamin E, and by giving 12 drams of wheat germ oil in 24 hours, he completely abolished the symptoms.[89] Shute[93b] refers to cases of pre-abruptios (probably the same as McKelney's "miniature premature separations"), which he diagnoses by finding areas of uterine tenderness to palpation. He states they disappear, only to recur, and *always* at the same site in the uterine wall. With these pre-abruptios may go the signs of early toxemia. Shute states that these areas of tenderness are frequently overlooked or wrongly diagnosed, often as appendicitis, "baby kicking," adhesions, and so forth. He further believes this uterine tenderness is almost *always the first sign of vitamin E deficiency in human pregnancy*, and that "it is always relieved by prompt administration of vitamin E." Such cases always show a high blood estrogen level and such an assay is "*sine qua non*" for diagnosis. In his later work he believes the dose required increases as the pregnancy proceeds, therefore, enough vitamin E must be given to control the symptoms rather than using any standard dose.[93b] He believes that vitamin E acts to neutralize the excess estrogenic substance which resists the intrusion of placental villi into the uterine wall. It leaves open the interesting possibility that toxemias of pregnancy may be due to dietary deficiency.

Male Sterility. Moench[63] has recently suggested the use of vitamin E in treating male sterility. Shute[92] reported 1 case of testes atrophy that returned to potency after vitamin E therapy, and also a case of testicular descent on vitamin E therapy after pregnancy urine had failed to produce this result. This seems, however, to be contrary to the attempts in rats to reverse testicular damage by giving vitamin E. Biskind and Falk[16b] have treated 11 cases of infertility in the male with vitamin B_1 and vitamin E in combination, and reported definite improvement in the number, motility and morphology of sperm in these people. Of these men, 8 succeeded in begetting children after treatment.

Congenital Anomalies. Often spontaneous abortions are associated with developmental anomalies of the fetus. Byerly[19] and Macomber[50] suggested that vitamin E deficiency is a factor in producing fetal deformities. Neither Vogt-Møller,[109–110] nor Watson[113] and Tew[113a] have reported any gross fetal anomalies in infants whose mothers were carried to term with wheat germ oil. Shute,[92] however, reported 2 anomalous fetuses in 29 pregnancies where the mother had been so treated. Currie[23–25] found 1 child, in a series of 21 cases treated with wheat germ oil, which died due to a structural defect.

One may thus accept the fact that failure of wheat germ oil therapy in these above mentioned conditions may be due to inadequate dosage, idiosyncrasy, hypothyroidism, seasonal depletion of vitamin E, rancid oil or abortions due to other causes than vitamin E deficiency.

INFLUENCE ON LABOR. Shute[91] showed that wheat germ oil used up to the onset of labor in no case prolonged the onset. Even the attempt to stop labor by massive dosage during the first stage was not successful.

DOSE. Danforth[27] says more is needed by the male to prevent testes changes than by the female to prevent "resorption" of the fetus. Eppstein[38] points out that absorption of vitamin E from the gut varies, and its destruction in the gut or in the tissues may be excessive, thus causing deficiency.

Currie[23-25] used 3 minims of wheat germ oil daily (in capsules) until the onset of labor. Macomber[50] showed that 500 mg. of wheat germ oil per day in 20% lard did not protect 44% of experimental rats, but that 20 gm. of lettuce per day did protect on the same diet. Shute[65] says that it should be given until the antiproteolytic factor has disappeared from the serum and continue with a dosage that will keep the serum normally digestible. He used 12 drams in the first 24 hours and 1 dram per day thereafter.[65,69,90] Later,[93b] he says that the dose should be the amount necessary to control symptoms of "pre-abruption" and to continue the drug to term. Vogt-Møller's clinic used 2 to 3 gm. per day with no special precautions to preserve its potency.[90] Three to 6 mg. per day are usually recommended in the treatment of threatened abortion.

POTENCY. Shute[91] showed that wheat germ oil that is not kept cold will lose its potency and thus signs of threatened abortion will return. In bulk or capsule form the oil retains its potency no longer than 8 days. Alpha tocopherol became ineffective when given with cod-liver oil.[82] Others[77] maintain that it can be kept in sealed vacuum cans for years and still retain potency. The preparation used most often is fresh ether extracted oil.

IDIOSYNCRASY. No toxic effect has been noted on 6 drams per day for 6 months. However 5 patients treated for vaginitis with wheat germ oil were sensitized and developed urticaria.[93] Shute[90] also had 5 adults and 1 infant who developed flatulence, hot flashes, urticaria, and nausea and vomiting who had been treated with vitamin E.

Summary and Conclusions. The present status of vitamin E may be summarized as follows:

1. The active principle of vitamin E is a polycyclic compound of the sterol type that possesses certain physical and chemical properties. Statements as to how such compounds are synthesized and their sources in nature are readily found in the literature. The relationship of vitamin E to anthracene derivatives has been established.

2. Whether growth and development are aided or not by vitamin E remains controversial.

3. That vitamin E has close relations with the endocrine systems of the body has been established, but its exact rôle has not yet been made clear.

4. Manifestations of vitamin E deficiencies (especially in rats) are retarded development and/or resorption of the fetus, and specific degeneration of the testis in males. Changes are reversible in the female. In the male the evidence is both insufficient and contradictory.

5. The mechanisms involved remain theoretical.

6. The correct use of vitamin E in humans, as far as reproduction is concerned, still remains to be gleaned from the future. However, certain facts seem apparent. Abruptio placentæ, if diagnosed early by the signs mentioned, is amenable to treatment with vitamin E. "The best therapy for abruptio is prevention and that is now possible" (Shute[93]). Likewise threatened abortion seems to respond favorably to vitamin E. The largest series of cases treated thus far are those of habitual abortion, and in these

the figures average 75% good results with vitamin E in some form or other. However, the difficulty in evaluating all such data is obvious—no controls are possible. We do not know whether the patient would abort this particular time even if wheat germ oil had not been used. Further the number of cases reported and studied are still too few to be of much value statistically. In the other pathologic conditions, reports are still fewer and too vague to have practical significance at this time. However, failure to substantiate such reports may well reside in the technical difficulty in preparing and preserving the potency of wheat germ oil, as has been pointed out.

Vitamin E therapy will probably never play the rôle that its fellow vitamins have played in other conditions. It should, however, be studied much further, experimentally and clinically in the pathologic conditions mentioned, especially as no other valuable or specific therapeutic measures exist, as it apparently does no harm and has the possibility of doing good. When the number of well-studied cases is sufficient to be statistically imposing, its true worth may be better evaluated. "It is easily possible that in stressing the relation of the tocopherols to reproduction we may be missing their basic function—growth of the fetus and maintenance of male germinal epithelium perhaps being but a small part of the whole."[114]

REFERENCES

(1.) Adamstone, F. B.: Arch. Path., 31, 603, 1941. (2.) Adamstone, F. B.: Ibid., 31, 613, 1941. (3.) Adamstone, F. B.: Ibid., 31, 622, 1941. (4.) Adamstone, F. B.: Ibid., 31, 706, 1941. (5.) Adamstone, F. B.: Ibid., 31, 711, 1941. (6.) Adamstone, F. B.: Ibid., 31, 717, 1941. (7.) Adamstone, F. B.: Ibid., 31, 722, 1941. (8.) Adamstone, F. B.: J. Morph., 52, 47, 1931. (9.) Adamstone, F. B., and Card, L. E.: Ibid., 56, 339, 1934. (10.) Adamstone, F. B.: Am. J. Cancer, 28, 540, 1936. (11.) Adamstone, F. B.: Science, 80, 450, 1934. (12.) Askew, F.: Biochem. J., 29, 472, 1935.

(13.) Bacharach, A. L.: The Vitamins, a Symposium, Chem. Publ. Company, p. 47, 1940. (14.) Bacharach, A. L., et al.: Biochem. J., 31, 2287, 1937. (15.) Bacharach, A. L.: Brit. Med. J., 1, 890, 1940. (16.) Barnum, G. L.: J. Nutr., 9, 621, 1931. (16a.) Biddulph, C., and Meyer, R. K.: Endocrinology, 30, 551, 1942. (16b.) Biskind, M. S., and Falk, H. C.: J. Clin. Endocrinol., 3, 148, 1943. (17.) Bradway, E., and Mattill, H. A.: J. Am. Chem. Soc., 56, 2405, 1934. (18.) Browne, F. J.: The Vitamins, a Symposium, Chem. Publ. Company, p. 82, 1940. (19.) Byerly, T. C., Titus, H. W., Ellis, N. R., and Landauer, W.: Proc. Soc. Exp. Biol. and Med., 32, 1542, 1935.

(20.) Copping, H. M.: The Vitamins, a Symposium, Chem. Publ. Company, p. 44, 1940. (21.) Csik, L.: Abstracted in Chem. Abst., 27, 2183, 1933. (22.) Cunningham, I. J., and Hopkirk, C. S. M.: Ibid., 30, 142, 1936. (23.) Currie, D. W.: The Vitamins, a Symposium, Chem. Publ. Company, p. 77, 1940. (24.) Currie, D. W.: Brit. Med. J., 1, 752, 1936. (25.) Currie, D. W.: Ibid., 2, 1275, 1935. (26.) Cuthbertson, W. F., McCutcheon, A., and Munro, H. N.: Biochem. J., 34, 34, 1940.

(27.) Danforth, W. C.: Illinois Med. J., 69, 219, 1936. (28.) Davidson, J. R.: Canad. Med. Assn. J., 31, 486, 1934. (28a.) DiBassi, W.: Virchows Arch. f. path. Anat., 275, 250, 1930. (29.) Drummond, J. C.: Vitamin E, a Symposium, Chem. Publ. Company, p. 27, 1940. (30.) Drummond, J. C., Singer, E., and Macwalter, R. J.: Biochem. J., 29, 456, 1935. (31.) Drummond, J. C., Singer, E., and Macwalter, R. J.: Ibid., 29, 2510, 1935. (32.) Drummond, J. C., Singer, E., and Macwalter, R. J.: Ibid., 29, 472, 1935. (33.) Drummond, J. C., Singer, E., and Macwalter, R. J.: Ibid., 31, 1852, 1937.

(34.) Emerson, O. H., Emerson, G. A., Mohammad, A., and Evans, H. M.: J. Biol. Chem., 129, 99, 1937. (35.) Emerson, O. H., Emerson, G. A., and Evans, H. M.: Science, 83, 421, 1936. (36.) Emerson, O. H., Emerson, G. A., and Evans, H. M.: J. Nutr., 14, 169, 1937. (37.) Emmerie, A. et al.: Vitamin E, a Symposium, Chem. Publ. Company, p. 14, 1940. (38.) Eppstein, S. H., and Morgulis, S.: Proc. Soc. Exp. Biol. and Med., 45, 715, 1940. (39.) Evans, H. M., and Burr, G. O.: J. Biol. Chem., 76, 273, 1929. (40.) Evans, H. M.: J. Am. Med. Assn., 99, 469, 1932. (41.) Evans, H. M., Emerson, O. H., and Emerson, G. A.: J. Biol. Chem., 113, 319, 1936. (42.) Evans, H. M., Murphy, E. A., Archibald, R. C., and Cornish, R. E.: Ibid., 108, 515, 1935. (43.) Fernholz, E.: J. Am. Chem. Soc., 59, 1154, 1937. (44.) Grijus, G., and Dingemanse, E.: Chem. Abst., 27, 3974, 1933. (44a.) Goettsch, M.: J. Nutr., 23, 513, 1942.

(45.) Haddow, A., and Russel, H.: Am. J. Cancer, 29, 363, 1937.

(46.) Jukes, T. H.: J. Nutr., 13, 382, 1937.

(47.) Karrer, P.: Vitamin E, a Symposium, Chem. Publ. Company, p. 9, 1940. (48.) Korenchevsky, V.: Chem. Abst., 30, 4204, 1936. (48a.) Kudrjaschow, B. A.: Endokrinol., 7, 91, 1930.

(48b.) League of Nations, Bulletin of the Health Organization of the, 9, 436, 413, 1940–41.

(49.) MacDonald, C. R.: Vitamin E, a Symposium, Chem. Publ. Company, p. 79, 1940. (50.) Macomber, D.: New England Med. J., 209, 1235, 1935. (51.) Makenzie, C. G., and McCallum, E. V.: J. Nutr., 19, 1940. (52.) Makenzie, C. G., and McCallum, E. V.: Ibid., 21, 225, 1941. (53.) Marchesi, F.: Chem. Abst., 29, 3895, 1935. (54.) Martin, G. J.: J. Nutr., 13, 679, 1937. (55.) Martino, G.: Chem. Abst., 30, 4546, 1936. (56.) Mason, K. E.: Vitamin E, a Symposium, Chem. Publ. Company, p. 31, 1940. (57.) Mason, K. E.: Am. J. Anat., 52, 153, 1933. (58.) Mason, K. E., and Bryan, W. L.: J. Nutr., 20, 501, 1940. (58a.) Mason, K. E.: Yale J. Biol. and Med., 14, 604, 1941–42. (58b.) Mason, K. E.: J. Nutr., 23, 59, 1912. (58c.) Mason, K. E.: Ibid., 23, 71, 1942. (59.) Mattill, H. M.: J. Am. Med. Assn., 89, 1505, 1927. (60.) Mattill, H. M.: Ibid., 110, 1838, 1938. (61.) McArthur, C. S., and Watson: Science, 86, 35, 1937. (62.) McCullagh, D. R.: Cleveland Clin. Quart., 8, 215, 1941. (63.) Moench, G. L.: Am. J. Obst. and Gynec., 32, 406, 1936. (64.) Moore, T.: Vitamin E, a Symposium, Chem. Publ. Company, p. 41, 1940. (65.) Moore, T.: Biochem. J., 34, 1321, 1940. (66.) Moore, T., and RaoRajogopal, K.: Ibid., 34, 335, 1940. (67.) Müller, J. H.: Chem. Abst., 31, 5025, 1937.

(68.) Nelson, W. O.: Anat. Rec., 56, 241, 1935.

(69.) Olcott, H. S., and Mattill, H. A.: J. Biol. Chem., 93, 59, 1931. (70.) Olcott, H. S., and Mattill, H. A.: Ibid., 93, 65, 1931. (71.) Olcott, H. S., and Mattill, H. A.: Ibid., 104, 423, 1934. (72.) Olcott, H. S., and Mattill, H. A.: Ibid., 107, 471, 1934. (73.) Olcott, H. S., and Mattill, H. A.: Ibid., 110, 659, 1935. (74.) Olcott, H. S., and Mattill, H. A.: Ibid., Proc. lxx, Vii, 114, 1936. (75.) Olcott, H. S., and Mattill, H. A.: J. Am. Chem. Soc., 58, 1627, 1936. (76.) Olcott, H. S., and Mattill, H. A.: J. Biol. Chem. Proc., 119, lxxiv, 1937. (77.) Olcott, H. S., and Mattill, H. A.: J. Nutr., 14, 305, 1937. (78.) Olcott, H. S., and Emerson, O. H.: J. Am. Chem. Soc., 59, 1008, 1937.

(79.) Palmer, L. S.: Ibid., Proc., 119, xxv, 1837.

(80.) Ridgeway, R. D., and Drummond, J. C.: Biochem. J., 34, 1569, 1940. (81.) Ringsted, A.: Biol. Abst., 9, 11407, 1935. (82.) Rowlands, I. W., and Singer, E.: J. Physiol., 86, 323, 1936. (83.) Rowntree, L. G., Steinberg, A., Dorrance, G. M., and Ciccone, E. F.: Am. J. Cancer, 31, 359, 1937.

(83a.) Schioppa, L.: Ztschr. f. Vitaminforsch, 8, 132, 1938–39. (84.) Shute, E.: Vitamin E, a Symposium, Chem. Publ. Company, p. 67, 1940. (85.) Shute, E.: J Obst. and Gynec. Brit. Emp., 42, 1071, 1935. (86.) Shute, E.: Ibid., 42, 1085, 1935. (87.) Shute, E.: Ibid., 43, 74, 1936. (88.) Shute, E.: Ibid., 44, 253, 1937. (89.) Shute, E.: Am. J. Obst. and Gynec., 33, 429, 1937. (90.) Shute, E.: Ibid., 35, 240, 1938. (91.) Shute, E.: Ibid., 35, 609, 1938. (92.) Shute, E.: Ibid., 35, 810, 1937. (93.) Shute, E.: Canad. Med. Assn. J., 37, 350, 1937. (93a.) Shute, E.: Ibid., 47, 350, 1942. (93b.) Shute, E.: Surg., Gynec. and Obst., 75, 515, 1942. (93c.) Silbernagel, W. M. and Burt, O. P.: Ohio State Med. J., 39, 430, 1943. (94.) Singer, E.: J. Physiol., 87, 287, 1936. (95.) Smith, L. I., Ungnade, H. E., Stevens, J. R., and Christman, C. C.: J. Am. Chem. Soc., 61, 2615, 1939. (96.) Smith, L. I., Ungnade, H. E., Stevens, J. R., and Christman, C. C.: Ibid., 64, 433, 1942. (97.) Smith, L. I., Ungnade, H. E., Stevens, J. R., and Christman, C. C.: Ibid., 64, 440, 1942. (98.) Smith, L. I., Ungnade, H. E., Stevens, J. R., and Christman, C. C.: Ibid., 64, 445, 1942. (99.) Smith, L. I., Ungnade, H. E., Stevens, J. R., and Christman, C. C.: Ibid., 64, 447, 1942. (100.) Stein, S. I.: J. Nutr., 9, 611, 1935. (101.) Sure, B.: J. Biochem., 63, 211, 1925. (102.) Sure, B.: Ibid., 76, 659, 1928. (103.) Szabo, I.: Endocrinology, 27, 125, 1940.

(104.) Todd, A. R.: Biochem. J., 31, 2217, 1937. (105.) Todd, A. R.: Vitamin E, a Symposium, Chem. Publ. Company, p. 3, 1940.

(106.) Underhill, S. W. F.: Ibid., p. 38, 1940. (107.) Urner, J. A.: Anat. Rec., 60, 175, 1931.

(108.) Vezar, F.: Proc. Staff Meet. Mayo Clinic, 4, 351, 1929. (109.) Vogt-Meller, P.: Lancet, 2, 182, 1931. (110.) Vogt-Meller, P.: Vitamin E, a Symposium, Chem. Publ. Company, p. 57, 1940.

(111.) Waddel, J.: J. Nutr., 4, 67, 1931. (112.) Waddell, J., and Steinbock, H.: Ibid., 4, 79, 1931. (113.) Watson, E. M.: Canad. Med. Assn J., 34, 134, 1936. (113a.) Watson, E. M., and Tew, W. P.: Am. J. Obst. and Gynec., 31, 352, 1936. (114.) Wilson, E.: Personal communication. (115.) Wright, M. D., and Drummond, J. C.: Biochem. J., 34, 32, 1940.

(116.) Zagami, V., and Sindoni, M.: Phys. Abst., 20, 755, 1926.

RADIOLOGY

THE PRESENT STATUS OF CONTRAST MYELOGRAPHY

By Harry M. Weber, M.D.

CONTRAST myelography consists of the use of some type of medium which when injected into the spinal subarachnoid space allows the roentgenologic visualization of that space. By this procedure the presence of intraspinal tumors and other pathologic processes which obstruct, distort or obliterate the subarachnoid space can be detected.

The intraspinal use of such an agent was suggested first by Dandy[12] in 1919 when he predicted that tumors of the spinal cord might be localized by the injection of air. The actual intraspinal use of air to detect and localize tumors causing complete block was reported by Dandy[13] in 1925. However, in 1922 Sicard and Forestier[35] had described the intraspinal injection of iodized oil for the roentgenologic visualization of obstructing intraspinal tumors and this method was received with much enthusiasm. Air myelography was more or less abandoned. Odin, Runström and Lindblom[30] in 1929, and Camp[8] in 1930 recommended the use of iodized oil to detect unobstructing lesions of the spinal canal. Iodized oil myelography became a well-known and generally accepted method for the diagnosis of intraspinal tumors when neurologic localization was unsatisfactory. This type of iodized oil we shall refer to by its trade name, lipiodol, to distinguish it from iodized oil of different character which has been developed recently.

In 1934 Coggeshall and von Storch[11] used air to visualize the lower part of the dural sac in 3 normal persons and suggested that by this method "deformities of the contour of the dural sac may be seen as they are produced by neoplasms, congenital deformities, or traumatic lesions." In the same year Van Wagenen[36] demonstrated the level of 3 cord tumors with block by the use of air. Thus, interest in air myelography began to develop again. In 1937 Reichert,[32] and Scott and Young[34] reported the roentgenologic visualization of protruded intervertebral disks by air myelography.

There is little doubt that lipiodol was found to be most accurate in the visualization of intraspinal tumors. Camp and Addington[9] in 1939 reported the results of lipiodol myelography in 417 cases. Discounting 5 cases in which there was a lesion below an anomalous cul-de-sac, they found lipiodol to be accurate in detecting and localizing the lesion in 96.8% of the cases. They also described 13 cases in which operation was performed and which had been considered negative after lipiodol myelography. This included the 5 cases in which there was anomaly of the cul-de-sac and in which protruded lumbosacral disks were found. In 2 of the remaining 8 cases there were protruded lumbosacral disks, in 4 thickened ligamentum flavum was found, and in 2 no lesion was found at operation. This report of surgical findings in cases considered negative by myelography is most important. Almost all of the papers which have appeared in the literature regarding myelography deal only with the

surgical findings in cases considered positive by myelography. The erroneous impression that may result from this type of analysis is obvious.

There have been other statements with regard to the accuracy of lipiodol which agree fundamentally with those of Camp and Addington. Hampton found lipiodol to be accurate in 93% of 133 cases. Bell and Spurling recommended lipiodol, as did Mixter[25] who warned that it must not be used promiscuously.

Camp[8] also has shown that with the use of lipiodol it is possible in many instances to determine whether a tumor of the spinal cord is extradural or intradural, and in the latter case whether the tumor is extramedullary or intramedullary. This is most important information if the tumor is a true neoplasm. He was able to identify the character of the lesion in 90.8% of his cases. It thus seems that for the accurate localization and gross identification of neoplasms of the spinal canal at any level lipiodol is the most trustworthy agent yet found.

There is some controversy as to the amount of oil necessary for diagnosis. There are many, for example Bell and Spurling, who feel that 2 cc. of lipiodol is sufficient. Others, for example Hampton, use a larger amount, usually about 5 cc. Camp[8] advised that 5 cc. be used since, in his opinion, with this amount small lesions are less likely to be missed than with a smaller amount, there is less danger of pseudo-arrests which simulate partially obstructing lesions, and the lipiodol does not break up so readily into globules in the thoracic and cervical regions.

With the larger quantity of lipiodol multiple tumors are found more easily, according to Camp.[7] Of 72 cases of tumors of the cord he found that 4% had multiple tumors. For this reason he emphasized that enough lipiodol must be used to allow examination of the entire canal. He expressed the opinion that 5 cc. is in reality no more irritating than 2 cc. and there is as much medico-legal objection to the small amount as there is to the larger amount. It should also be kept in mind that in a few days or weeks after injection the column of lipiodol breaks up more easily into globules and therefore the examination is most satisfactory immediately after the injection.

Since lipiodol was received with such enthusiasm at first and since its accuracy has been proved, there must be some reason for the further search for another agent to supplant it in contrast myelography. At first lipiodol was used too freely and rather promiscuously. Reactions were reported as the result of its irritating effect. There has been a great deal of experimental and clinical work in this respect and this has been well reviewed by Brown and Carr,[5] Marcovich, Walker and Jessico,[31] and Garland.[13] There is no doubt that there is often an immediate reaction within 24 hours after the injection. This may consist of any or all of the following: headache, fever, nausea, vomiting and stiff neck. The spinal fluid shows slight or moderate pleocytosis. Marcovich and his associates stated that these symptoms are gone within 72 hours. Love and Walsh[22] reported this early reaction and said: "We have seen no clinical reaction to iodized oil that might not have been produced by a spinal or cisternal puncture with the withdrawal of spinal fluid alone."

Camp[8] and Hampton[17] have warned that only fresh lipiodol may be used safely. At times aggravation of the patient's symptoms occurs after the injection of lipiodol but that also occurs when only a spinal puncture is done.

It is generally accepted now that a definite contraindication to the use of lipiodol is the presence of an inflammatory process involving the cord, brain or meninges.

So far as the delayed effect of lipiodol is concerned there is more controversy. Much of the experimental work done on animals would indicate that there results chronic arachnoiditis at least. There are some reports of actual damage to the cord. It seems that in many of these experiments on animals relatively larger quantities of lipiodol were used than are ever used for human patients. It also would seem that in some of the experiments the chronic arachnoiditis described might be due partially to the surgical procedures used in the experiments rather than being entirely ascribable to the lipiodol. In the majority of instances in which patients were followed for many months or several years after the injection little definite evidence could be found to indicate disability due to the presence of the lipiodol. Adson[1] has observed infrequently a symptom which, in his opinion, is due to residual lipiodol. That is sacral pain when the patient is standing. This pain is relieved when the lipiodol is removed.

Many of the cases reported which do show detrimental effect are cases in which the injection was made in the presence of an inflammatory process, or in which chronic arachnoiditis was present when the oil was injected. It does appear that when there is preëxisting chronic arachnoiditis this process is made worse by the permanent presence of lipiodol. On the other hand, Marcovich and his associates[24] mentioned that in some cases in which arachnoiditis develops after lipiodol myelography followed by operation, the arachnoiditis may be the result of bleeding which occurred during or after the operation rather than of the lipiodol. They concluded that "although the changes in the spinal cord and its membrane in animals after intrathecal injection of iodized oil are fairly severe, the constant pathologic changes—a slight proliferation of the arachnoid membrane with a few fine dural adhesions—in the human spinal cord following the injection of iodized oil are minimal. Constant parenchymal changes are not present."

Lipiodol remains permanently unless it is removed promptly after its injection. Within a relatively short period it begins to extend along the nerve sheaths in the lumbar and sacral regions. This part of the lipiodol is fixed in the tissues but most of the oil remains free in the arachnoid sac unless the membranes have been opened during operation, in which case some of the lipiodol escapes into the epidural tissues where it becomes fixed. As the result of free movement of the lipiodol in the subarachnoid space Garland, as well as Marcovich and his associates, reported droplets of oil in the basal cisterns. Garland's cases showed some fixation of the oil there while in the cases of Marcovich the oil was free. In none were there any resulting symptoms.

The fact that lipiodol remains permanently is one of the greatest objections to its use. This has been well stated by Camp,[8] ". . . . the history of many patients suffering from conditions of the back is complicated by injuries and insurance or medico-legal entanglements . . . . Resourceful attorneys and malingering patients may use roentgenograms which reveal the shadow of the remaining oil as a tangible basis for claiming aggravation of symptoms and such roentgenograms may have a profound effect on a sympathetic jury."

To overcome this objection there have been endeavors to remove lipiodol immediately after the examination. In 1936 Lucherini[23] first attempted to do this with some success. Later Adson[1] and Briesen[4] reported methods for the removal of lipiodol. Perhaps the most successful method has been that of Kubik and Hampton.[21] Briefly, this consists of the gentle aspiration of the lipiodol through a large needle. This has been used by others with considerable success. However, it is quite time-

consuming, many times it is not completely successful, and sometimes it is quite unsatisfactory. The complete removal of the lipiodol is usually not possible when the dura is opened during operation, although many times much of the oil can be removed. It does happen at times that lipiodol is injected accidentally into the epidural space. This has been studied by Hamby[16] who found that factors which tend to reduce the spinal fluid pressure, especially previous spinal puncture or air myelography, predispose to misplacement of lipiodol. Lipiodol which has been injected epidurally cannot be removed.

Thus we find that lipiodol yields very accurate results, it allows the examination of the entire canal, the roentgenoscopic examination can be repeated later if desired, and it will not only localize the lesion but many times will suggest the type of lesion present. On the other hand, lipiodol may cause some irritation of the meninges, its removal is difficult, and the medico-legal aspects of its use must always be considered.

The value of lipiodol in the diagnosis of true neoplasms of the spinal canal cannot be denied, but there has been discovered a different type of lesion of the spinal canal which has stimulated the attempt to replace lipiodol with some other medium. This mass, whose importance has been recognized only in the last several years, is the protruded intervertebral disk. According to Love and Walsh,[22] 96% of protruded intervertebral disks are found in the lumbar region and of these by far the greater part occur at the last two lumbar interspaces; 90% according to Scott and Young.[34] It is chiefly for this type of lesion that the use of air or oxygen myelography has developed. Air has also been used to define the level in cases of complete spinal block.

Ordinarily, however, air myelography visualizes only the lumbar region and is of no value above the 10th dorsal segment unless there is a block above this segment, according to Camp.[8] As he has stated, there are certain advantages to its use: "(1) there is no contraindication; (2) the air or oxygen is absorbed after the examination; (3) there is no irritating effect from the injection other than that resulting temporarily from the injection; (4) roentgenoscopic examination is not necessary and since the findings are recorded on roentgenograms these may be studied at the examiner's convenience." Camp has enumerated the following disadvantages: "(1) the procedure is unsatisfactory for non-obstructing lesions above the level of the conus medullaris; (2) the shadows produced with air and defects revealed by it are less distinct than those observed when iodized oil is used, their interpretation is correspondingly more difficult and unless the examiner is experienced in the procedure the likelihood of error is greatly increased; (3) the roentgenoscopic verification of any defect is not possible; (4) inconclusive results of examination are much more frequent when air is used than when iodized oil is used; (5) experience has shown the results of studies made with air (especially when such results are negative) are less accurate than the results obtained with iodized oil."

There are many who feel that the method with air is quite reliable. Chamberlain and Young[19] reported 300 cases and "in every case in which operation was performed the level of the lesion predicted after myelography examination was verified at laminectomy. Air studies have not been misleading as there were no instances in which the myelogram indicated a lesion without verification at operation." Poppen[33] also considered air myelography quite reliable and reported 175 cases in which the diagnosis of protruded disk was made and in 150 of which the diagnosis was confirmed at operation. It was Poppen who first used oxygen instead of air in

myelography. Oxygen is more rapidly absorbed than air and therefore there is less distress after its use. Oxygen is now used instead of air very frequently. Scott and Young also reported favorably for the use of air myelography. However, in none of these series has there been a report of the results of operation in those cases considered negative by air myelography. Camp[8] found air to be 83% accurate in those in which there were positive myelographic findings and in which operation was performed. However, he found that of those patients on whom operation was performed despite a negative finding by air myelography 77% had lesions. Hampton estimated that air will permit diagnosis of only about 50% of disks. He stated, "Air myelography is of distinct value when the findings are unequivocally positive, but it is of little value when the findings are equivocal or negative."

There is no question that air myelography has definite value but it is most important that its limitations be understood clearly. In cases of suspected protruded intervertebral disk a thorough understanding of the symptoms and neurologic signs associated with that condition is most essential. That aspect of the diagnosis is of greater importance than the roentgenologic examination. Camp and Addington[9] have shown that low backache with sciatica occurs in a fairly high percentage of cases in which there are tumors of the cervical or thoracic portion of the spinal cord. Therefore low backache and sciatica alone are not enough to justify the diagnosis of protruded lumbar intervertebral disk nor to warrant air myelography. The promiscuous use of air myelography for patients who have not had the proper thorough clinical and neurologic work-up is most dangerous and thus many patients may be submitted to unnecessary and therefore harmful surgical intervention.

Bradford and Spurling[3] have stated that "although the presence of a spinal neoplasm is unequivocally an indication for surgical removal when possible, the presence of posterior herniation of the nucleus pulposus is not an indication for surgical removal unless it has produced incapacitating radicular symptoms." This statement has been supported by the work of Horwitz[19] who has found, through anatomic studies, the following asymptomatic conditions simulating protruded disks at myelography: (1) posterior bulging of the entire intervertebral disk without localized herniation is a common finding in adult cadaver material; (2) degeneration of the intervertebral disk with subsequent narrowing of the intervertebral space may be associated with a settling of the upper vertebral body downward and backward on the vertebral body below, so that the postero-inferior surface of the vertebral body and the overlying disk material project posteriorly into the neural canal. This "posterior displacement" may be exaggerated by bony proliferation of this postero-inferior margin; (3) apparent bulging of the ligamentum flavum of normal thickness as result of marginal bony proliferation of the underlying facets of the apophyseal joints.

These false deformities apply both to lipiodol myelography and to air myelography but this is especially to be remembered with regard to air myelography since that method is being used so freely in the diagnosis of protruded intervertebral disk.

As has been suggested by many investigators and undoubtedly applied in many instances, it appears most logical and if after a complete clinical and neurologic examination a protruded intervertebral disk in the lumbar region is suspected air myelography should be used. If a definite deformity is found at a level that is in keeping with the neurologic findings, then

the diagnosis of protruded disk at that level can be made. As a matter of fact, slight deformities which appear in the air myelogram can be given a limited significance if these deformities are compatible with the neurologic findings. If, however, the findings in the air myelograms are not definite or not exactly compatible with the neurologic findings, lipiodol myelography should be employed. This applies also if the air myelogram is negative and the clinical picture is suggestive of a protruded disk.

It must be accepted, as shown by Hampton and Robinson,[18] that even with the use of lipiodol there may be a protrusion of the intervertebral disk at the 5th lumbar interspace which will produce a minimal defect or none in the lipiodol column. Anomalies of the cul-de-sac as described by Camp and Addington[9] will make the diagnosis of protruded lumbosacral disk impossible by myelography. It has been shown that protrusion of the intervertebral disk may be intermittent and if myelography is performed when the disk is not protruding the myelogram will, naturally, fail to show the lesion. Thus, we must accept the fact that protrusion of the intervertebral disk can occur without myelographic evidence. This emphasizes the importance of the clinical and neurologic examination.

Dandy[14] recently has advocated the abolition of all contrast myelography in the diagnosis of protruded intervertebral disk. In many places now, in cases in which the clinical picture is typical and clear-cut, these patients are being operated on without preliminary myelography and with excellent results. It seems that this is applicable only to typical cases and there are many cases which are not quite typical in certain respects but in which the patients are found by myelography to have protruded disks and obtain relief by surgical intervention. Dandy opposed myelography because he said that small disks and "concealed disks" are not seen at that examination. We must frankly acknowledge that no method of contrast myelography is always correct, and if the clinical and neurologic picture is quite typical and exact, then surgical exploration is indicated. This has been done in many cases, as reported by Camp, but this does not discount the value of myelographic confirmation in questionable cases.

In 1934 Lucherini[23] described thorotrast myelography. In 1938 in this country Nosik and Mortensen[29] reported using 4 cc. of a 25% solution of thorium dioxide. Later, papers appeared by Nichols,[25] Bunts,[6] and Nichols and Nosik.[27] There is no doubt that a most excellent visualization of the lumbar subarachnoid space is obtained in this manner. Thorotrast is miscible with the spinal fluid and gives a clear-cut outline, even showing each nerve sheath almost perfectly. Nosik[28] in 1943 reported his results with this medium. His positive diagnoses were found to be 93.7% correct. There was found to be 11.1% error when the myelographic diagnosis was negative. The thorotrast is removed by forced spinal drainage, using the method of Kubie and Retan.[20] Ten to 15% of the thorotrast remains as a rule and this amount is considered by the Council on Pharmacy and Chemistry of the American Medical Association not to have sufficient radioactivity to produce deleterious effects and to be too feeble to have physiologic significance.

Even if one is to accept as a fact this contention that the residual thorotrast is absolutely harmless, there is a greater objection to this medium, and that is the effect of accidental epidural injection of the solution. Epidural injection occurs occasionally with lipiodol and with air. One must expect it to happen with thorotrast at times. Thorotrast is extremely irritating to the tissues and after such an accident it cannot be removed. Certainly the medico-legal aspect of such an occurrence cannot

be minimized. Another objection to thorotrast is that only the lumbar segments and many times only the lower 3 lumbar segments are visualized. With thorotrast defects cannot be checked by roentgenoscopy, since it casts too faint a shadow to be seen in that manner. Forced spinal drainage causes distress and is a troublesome procedure.

Sanford and Doub[33] have devised a method, called epidurography, whereby air is injected into the epidural space in the lumbar region. In this way the localized protrusion of the disk is well shown in the lateral view. The main objection to this procedure is the technical difficulty, which is greater than with other methods of myelography. There may also be danger in injecting air into the vascular bed of the epidural space. The method is of use only in the lumbar region and only for protruded intervertebral disks.

Quite recently a new contrast medium called "Pantopaque" has been introduced. As yet there have been no reports as to its diagnostic value. However, a limited experience with its use may allow one to suggest some of its probable possibilities and limitations. This material is an iodized oil which is lighter than lipiodol. Since the weight and viscosity are less than those of lipiodol it can be aspirated from the arachnoid sac more easily and quite rapidly. By using a reasonable amount of care most of the pantopaque can be aspirated from the sac immediately after the examination, using the needle through which it was injected. It is said that the material which remains after aspiration gradually becomes less opaque until finally it is no longer visible roentgenographically. Pantopaque in the lumbar region resembles lipiodol. The shadow cast is similar to that produced by lipiodol and the material is manipulated in a manner similar to lipiodol. Roentgenoscopic as well as roentgenographic examination is used.

The main disadvantage is that pantopaque is light and not very viscid. For that reason small defects may be missed and false defects may be produced. Because of the low viscosity the material breaks up into globules very easily after it gets above the conus medullaris. This may make the examination of the dorsal and cervical regions less satisfactory. It would appear, after very limited experience with pantopaque, that it may be an improvement over air myelography for the examination of the lumbar region but may not be completely satisfactory for the examination of the canal above the lumbar region.

Conclusions. 1. A completely satisfactory medium for contrast myelography has not yet been discovered.

2. For accurate examination of the entire spinal canal, lipiodol remains the most satisfactory agent. There are objections to its promiscuous use, however.

3. Air myelography has limited but definite value, mostly for the examination of the lumbar region to detect protruded intervertebral disks.

4. The clinical and neurologic picture is most important in the diagnosis of protruded intervertebral disk. Contrast myelography has value only when the findings are compatible with the clinical and neurologic impression.

5. "Pantopaque" is a useful contrast agent; but its value cannot yet be determined because of insufficient experience with it.

REFERENCES

(1.) Adson, A. W.: Personal communication to the authors. (2.) Bell, J. C., and Spurling, R. G.: Radiology, 31, 473, 1938. (3.) Bradford, F. K., and Spurling, R. G.:

The Intervertebral Disc With Special Reference to Rupture of the Annulus Fibrosus With Herniation of the Nucleus Pulposus, Springfield, Ill., Charles C Thomas, 1941, 151 pp. (4.) Briesen, H. V.: Am. J. Roentgenol., 42, 525, 1939. (5.) Brown, H. A., and Carr, J. L.: Surg., Gynec. and Obst., 68, 915, 1939. (6.) Bunts, A. T.: Radiology, 36, 601, 1941. (7.) Camp, J. D.: Am. J. Roentgenol., 36, 775, 1936. (8.) Camp, J. D.: Med. Clin. North America, 25, 1067, 1941. (9.) Camp, J. D., and Addington, E. A.: Radiology, 33, 701, 1939. (10.) Chamberlain, W. E., and Young, B. R.: J. Am. Med. Assn., 113, 2022, 1939. (11.) Coggeshall, H. C., and von Storch, T. J. C.: Arch. Neurol. and Psychiat., 31, 611, 1934. (12.) Dandy, W. E.: Ann. Surg., 70, 397, 1919. (13.) Dandy, W. E.: Ann. Surg., 81, 223, 1925. (14.) Dandy, W. E.: J. Am. Med. Assn., 120, 605, 1942. (15.) Garland, L. H.: Radiology, 35, 467, 1940. (16.) Hamby, W. B.: Radiology, 37, 343, 1941. (17.) Hampton, A. O.: Arch. Surg., 40, 444, 1940. (18.) Hampton, A. O., and Robinson, J. M.: Am. J. Roentgenol., 36, 782, 1936. (19.) Horwitz, T.: Am. J. Roentgenol., 49, 199, 1943.

(20.) Kubie, L. S., and Retan, G. M.: J. Am. Med. Assn., 101, 354, 1933. (21.) Kubik, C. S., and Hampton, A. C.: New England J. Med., 224, 455, 1941. (22.) Love, J. G., and Walsh, M. N.: Proc. Staff Meet., Mayo Clin., 13, 792, 1938. (23.) Lucherini, T.: Riv. osp., 24, 475, 1934. (24.) Marcovich, A. W., Walker, A. E., and Jessico, C. M.: J. Am. Med. Assn., 116, 2247, 1941. (25.) Mixter, W. J.: Ann. Surg., 106, 777, 1937. (26.) Nichols, B. H.: Radiology, 38, 679, 1942. (27.) Nichols, B. H., and Nosik, W. A.: Radiology, 35, 459, 1940. (28.) Nosik, W. A.: Am. J. Roentgenol., 49, 214, 1943. (29.) Nosik, W. A., and Mortensen, O. A.: Am. J. Roentgenol., 39, 727, 1938. (30.) Odin, M., Runström, G., and Lindblom, A.: Acta radiol., (Suppl.), 7, 1, 1929. (31.) Poppen, J. L.: New England J. Med., 223, 978, 1940. (32.) Reichert, F. L.: J. Am. Med. Assn., 109, 1270, 1937. (33.) Sanford, H., and Doub, H. P.: Radiology, 36, 712, 1941. (34.) Scott, M., and Young, B. R.: Arch. Neurol. and Psychiat., 38, 1126, 1937. (35.) Sicard and Forestier: Bull. et mém. Soc. de chir. de Paris, 46, 463, 1922. (36.) Van Wagenen, W. P.: Ann. Surg., 99, 939, 1934.

BOOK REVIEWS AND NOTICES

NUTRITION AND CHEMICAL GROWTH IN CHILDHOOD. Vol. I, Evaluation. By ICIE G. MACY, PH.D., Director of the Research Laboratory of the Children's Fund of Michigan. Pp. 432; 66 figs. Springfield, Ill.: Charles C Thomas, 1942. Price, $5.00.

THE Reviewer regrets that it is not possible to do justice to this isolated first volume of the complete monograph on the work of Dr. Macy Hoobler and her associates of The Children's Fund of Michigan. Careful study of this book makes it evident that the whole project was more comprehensive than even the numerous individual papers which have appeared in the past decade indicated. This contribution to the literature is so notable that the Reviewer undertakes the analysis with hesitation, fearing lest he underestimate its value.

Furthermore a complete evaluation of the project and the data must depend not only upon the present book, but also on the second volume yet to be published.

The present volume presents the outline and organization of the project, the methods utilized to secure data together with their mathematical treatment, a critique of this and all research projects concerned with chemical and metabolic balance studies, and finally representative data selected from all aspects of the work illustrative of results and relationships. In short this work represents the most complete, the most meticulous and probably the most thoroughly reliable study of biochemical growth in childhood.

Naturally it was fortunate that there was available an organization such as the adjacent Methodist Children's Village in which the subjects to be studied could live under conditions approximating home life and at the same time provide assurance that food and fluid intakes would be controlled and all specimens collected according to plan.

The investigation of nutrition and chemical growth individual included study of the intake, utilization and excretion of 18 chemical substances by children taken to be as normal as the most reliable selective methods could determine them. Eleven children aged 4 to 10 years were studied first over a period of 95 days; 4 years later 11 subjects aged 55 to 104 months were investigated for 225 days, and 4 years later 7 of the same subjects were again restudied for 55 days. (It is most unfortunate that previous reviews have indicated that the studies were carried out on 29 *separate* individuals, thus failing to emphasize the serial study of the same children, which enhances the value of the whole contribution.)

Although the balance studies comprise the major portion of the work presented here, there are also numerous studies of the physiologic, including roentgenologic, and chemical aspects of digestion and excretion. Energy metabolism is presented in relation to protein, fat, carbohydrate and to the requirements for normal growth.

There is an interesting and significant chapter on the several chemical elements of the blood with partition between serum, plasma and cells. The studies on the cells are particularly stimulating since this field promises to be fruitful of research in the growth and metabolism of living mammalian cells, of which blood cells may be taken as fairly representative.

The chemical methods used are given in detail; those selected for these studies being the most practical and yet the most precise. To facilitate the completion of quantitative determinations as numerous as were required in this project, and to ensure greater coördination of results of administrative procedures, the polorograph and the spectograph were used. The utilization of the polorograph in research of this type is succinctly outlined. These sections are most valuable and will be used for future reference.

There is a brief but adequate section concerned with the methods of compilation and mathematical treatment of the experimental data with significant examples.

A fairly complete and entirely satisfactory bibliography of the literature of related research and this page index are accurate and adequate.

Dr. Macy and her associates are to be congratulated and one awaits with interest the publication of the second volume since the complete monograph is a great accumulation of facts and will be indispensable to pediatricians and investigators alike.   E. T.

THE SONNETS OF SHAKESPEARE. A Psycho-Sexual Analysis. By H. McCLURE YOUNG. Pp. 121. Copyrighted 1937 by H. McClure Young, 217 Exchange National Bank Bldg., Columbia, Mo. Price, $2.00.

THIS is an interesting, critical analysis of the thesis that the *Sonnets* express the poet's reaction to a love triangle that developed between him, his mistress, and his patron, Henry Wriothesly, Earl of Southampton. It is assumed that these *Sonnets* are numbered in the same orderly sequences in which they were written, and that thus they can be dated between 1596 and 1603, and the identity of the young man of the first series and his escape from execution be established. No light is thrown "on the identity of the Dark Lady, and but little on that of the Rival Poet and the affable familiar ghost." The study throws more light, if the author's plausible deductions are correct, on textual meaning and on Shakespeare's personality than on psycho-sexual problems. The booklet is recommended more to those interested in borderline medico-literary topics than to students of psychiatry.   E. K.

AN ATLAS OF ANATOMY. VOL. I. UPPER LIMB, ABDOMEN, PERINEUM, PELVIS, LOWER LIMB. By J. C. BOILEAU GRANT, M.C., M.D., CH.B., F.R.C.S. (EDIN.), Professor of Anatomy, University of Toronto. Pp. 214; 227 illus. Baltimore: The Williams & Wilkins Company, 1943. Price, $5.00.

THIS is the first volume of a projected 2-volume atlas of human anatomy. The half-tone illustrations are of dissections and line drawings, both types having color added where emphasis was indicated. Many of the views selected for illustration are similar to those seen by students in the course of classroom dissection, the illustrations being, in general, of regions rather than systems. The drawings were obviously made by a skilled artist, with gratifying attention to accuracy. For classroom use it is unfortunate that the arrangement on the page of some plates necessitates turning the book sideways. No regular descriptive text accompanies the plates. However, on each page the author has with appropriate brief observations and comments directed the reader's attention to salient points. The Birmingham revision of the nomenclature is used throughout, but where this differs substantially from the BNA both terms are given. There is a freshness of viewpoint about this atlas which makes it a fitting companion volume for the author's previously published textbook. In this Reviewer's opinion it will occupy an important place among books readily available for students of anatomy, whether they be in the classroom or in practice.   R. W.

DOCTOR PRYOR: AN AUTOBIOGRAPHY. By DR. J. W. PRYOR. Pp. 312; 17 illus. Cynthiana, Ky.: The Hobson Press, 1943. Price, $3.00.

ALMOST all successful physicians have had full lives that have included much of human interest. Relatively few, however, can extract from their experiences a narrative that deserves to appear in print. Biographies are, with extremely few exceptions, more instructive and more revealing than autobiographies.

This autobiography, to the Reviewer, holds a mid-position and is worth printing as a simple, honest presentation of the life of a simple honest medical teacher and practitioner that has influenced many others toward the good, and is typical of thousands of the better physicians of this country. It is not surprising that a distinct cross-sectional view of medical life in the Mississippi Valley through the latter part of its formative period emerges. We may hope, then, with the author that it will interest and inspire many, though in a different way from the great accounts of great figures such as those of Pasteur and Osler.

The offset style of type has good readability and comeliness and is highly appropriate for a wartime publication. There are fewer than the average number of typographical errors.   E. K.

A SYNOPSIS OF CLINICAL SYPHILIS. By JAMES KIRBY HOWLES, B.S., M.D., M.S., Professor of Dermatology and Syphilology, and Director of the Department, Louisiana State University School of Medicine; Senior Visiting Physician, Charity Hospital of Louisiana at New Orleans; Visiting Physician, French Hospital, Mercy Hospital, Hotel Dieu, Southern Baptist Hospital and Touro Infirmary. Pp. 671; 121 illus., 2 color plates: St. Louis: C. V. Mosby Company, 1943. Price, $6.00.

As the flood of compends on various subjects continues unabated, it is necessary, in fairness to the authors, that these volumes be considered individually from the standpoint of an attempt to condense masses of material into a small space rather than as more complete treatment of the subject. Viewed from this angle, Dr. Howles' "Synopsis of Clinical Syphilis" can be taken as a handy, conservative, usually impersonal discussion of syphilology with a working bibliography, concise chapter summaries and adequate differential lists.

The illustrations are generally good but have a tendency to emphasize unintentionally, of course, the erroneous belief that syphilis is chiefly a disease of negroes (*J. Am. Med. Assn.*, 122, 365, 764, 1943). This peculiarity of Dr. Howles' book is obviously due to the locus of his practice (Charity Hospital, New Orleans). Casual performance of serologic tests in the doctor's office is poor syphilologic practice, yet on page 149 the author recommends the Johns modification of the Meinicke-Butler test for office use. On page 281 and page 285 is a detailed description of syphilis of the hair and scalp but no mention of alopecia associated with neurosyphilis. Although there is a section on latent or asymptomatic syphilis, there is no adequate stress on the increasing number of patients who are apparently asymptomatic (symptomless) from the very inception of their infection.

This book, except for the limitations demanded by brevity, may be evaluated as a fair discussion of clinical syphilis.   H. B.

CLINICAL PARASITOLOGY. By CHARLES F. CRAIG, M.D., M.A. (HON.), F.A.C.S., F.A.C.P., Col., U. S. Army (Retired), D.S.M., Emeritus Professor of Tropical Medicine in The Tulane University of Louisiana, New Orleans; and ERNEST C. FAUST, M.A., PH.D., Professor of Parasitology in the Department of Tropical Medicine, The Tulane University of Louisiana. Third ed. Pp. 767; 284 illus., 4 colored plates. Philadelphia: Lea & Febiger, 1943. Price, $9.00.

THE third edition of this very useful text is entirely comparable in excellence to the two earlier ones. Four full-page colored plates, which illustrate the morphology of the organisms of malaria in thin and thick blood smears and the additions to the section of Arthropod parasites, greatly increase its value. It may be said again that the book is certainly the equal of any in the field.   H. R.

NEW BOOKS

Fundamental Exercises for Physical Fitness. By CLAIRE COLESTOCK, A.B., M.A., Assistant Director of Physical Education, City Schools, Pasadena, Calif.; and CHARLES LEROY LOWMAN, M.D., F.A.C.S., Chief of Staff, Orthopædic Hospital, Los Angeles, Calif. Pp. 314; 72 figs. New York: A. S. Barnes & Co., 1943.

Nervousness, Indigestion, and Pain. By WALTER C. ALVAREZ, M.D., Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant in the Division of Medicine, The Mayo Clinic, Rochester, Minn. Pp. 488. New York: Paul B. Hoeber, Inc., 1943. Price, $5.00.

Reaction to Injury. Pathology for Students of Disease Based on the Functional and Morphological Responses of Tissues to Injurious Agents. By WILEY D. FORBUS, M.D., Professor of Pathology, Duke University and Pathologist to the Duke Hospital. Pp. 797; 532 illus. (20 in color). Baltimore: The Williams & Wilkins Company, 1943. Price, $9.00.

Doctor in the Making. The Art of Being a Medical Student. By ARTHUR W. HAM, M.B., Associate Professor of Anatomy, in Charge of Histology, Faculty of Medicine, University of Toronto; Honorary Secretary of the Banting Research Foundation; and M. D. SALTER, M.A., PH.D., Lecturer and Research Fellow in the Department of Psychology, Faculty of Medicine, University of Toronto. Illustrations by JEAN MCCONNELL. Pp. 179. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $2.00.

Victories of Army Medicine. Scientific Accomplishments of the Medical Department of the United States Army. By EDGAR ERSKINE HUME, Colonel, Medical Corps, United States Army. Pp. 250; 2 plates (1 in color). Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $3.00.

Convulsive Seizures. How to Deal with Them. A Manual for Patients, Their Families and Friends. By TRACY J. PUTNAM, M.D., Professor of Neurology and Neurosurgery, College of Physicians and Surgeons, Columbia University; Director of Services of Neurology and Neurosurgery, Neurological Institute of New York. Pp. 169; 12 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $2.00.

Medical Clinics on Bone Diseases. A Text and Atlas. By I. SNAPPER, M.D., Formerly Professor of Medicine, Peiping Union Medical College, Peiping, China. Pp. 225; 30 plates. New York: Interscience Publishers, Inc., 1943. Price, $10.75.

Treatment of Experimental Data. By ARCHIE G. WORTHING, University of Pittsburgh; and JOSEPH GEFFNER, Weirton Steel Company. Pp. 342; 13 tables; many figs. New York: John Wiley & Sons, Inc., 1943. Price, $4.50.

Essentials of Proctology. By HARRY E. BACON, B.S., M.D., F.A.C.S., F.A.P.S., Professor and Head of the Department of Proctology, Temple University Medical School and Hospital; Head of Department of Proctology, St. Mary's Hospital; Consulting Proctologist, Rush Hospital, National Stomach Hospital, Douglass Hospital, Mercy Hospital and Paul Kimball Hospital, Lakewood, N. J.; Fellow, International College of Surgeons. Introduction by CURTICE ROSSER, B.A., M.D., F.A.C.S., F.A.P.A., Professor of Proctology, Baylor University, Dallas, Texas. Pp. 345; 168 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $3.50.

Hypertension. By IRVINE H. PAGE, A.B., M.D., Director, Lilly Clinic, Indianapolis City Hospital. Pp. 80; 7 figs. Springfield, Ill.: Charles C Thomas, 1943. Price, $1.50.

Medical Clinics of North America. Symposium on Specific Methods of Treatment. Boston Number. Pp. 245. Philadelphia and London: W. B. Saunders Company, 1943. Price, $16.00 per year.

Biochemistry of the Fatty Acids and Their Compounds, the Lipids. By W. R. BLOOR, Professor of Biochemistry and Pharmacology, The University of Rochester, Rochester, N. Y. American Chemical Society Monograph Series. Pp. 386; tables and charts. New York: Reinhold Publ. Corp., 1945. Price, $6.00.

Handbook of Tropical Medicine. By ALFRED C. REED, M.D., Associate Clinical Professor of Medicine, Stanford University School of Medicine; and J. C. GEIGER, M.D., Director of Public Health, San Francisco, Calif. Pp. 188. Stanford University, Calif.: Stanford University Press, 1943. Price, $1.50.

Atlas of Orthopedic Pathology. By D. M. ANGEVINE, Major, Medical Corps, A.U. S., and J. E. ASH, Colonel, Medical Corps, U. S. A., Curator. Prepared at the Army Medical Museum, Office of the Surgeon-General, U. S. Army from material in the Registry of Orthopedic Pathology. Sponsored by the American Academy of Orthopedic Surgeons and the American Board of Orthopedic Surgery, 1943. Pp. 91; many plates. Washington, D. C. Price, $5.00. Requests should be addressed to The Curator, Army Medical Museum, Washington 25, D. C.

Proceedings of the Rudolf Virchow Medical Society in the City of New York. Vol. I. Edited by the Publication Committee, FRANZ M. GROEDEL, M.D., and BRUNO KISCH, M.D. Pp. 76 (1942). Published by Brooklyn Medical Press, Inc., New York (1943). Price, $1.00.

> THIS new periodical contains 35 articles on miscellaneous subjects, mostly by ex-Germans, that were contributed to the 1942 meetings of the Virchow Society, formerly the Deutscher medizinischer Leseverein von New York. E. K.

Synopsis of Tropical Medicine. By SIR PHILIP MANSON–BAHR, C.M.G., D.S.O., M.D., F.R.C.P., Senior Physician to the Hospital for Tropical Diseases, Royal Albert Dock and Tilbury Hospitals; Consulting Physician in Tropical Diseases to the Dreadnought Seamen's Hospital, London; Director, Division of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine; Consulting Physician to the Colonial Office and Crown Agents for the Colonies; Consultant in Tropical Medicine to the Admiralty and to the Royal Air Force, etc. Pp. 224; 5 plates. Baltimore: The Williams & Wilkins Company, 1943. Price, $2.50.

Microscopic Technique in Biology and Medicine. By E. V. COWDRY, Professor of Anatomy, Washington University, and Director of Research, The Barnard Free Skin and Cancer Hospital. Pp. 206. Baltimore: The Williams & Wilkins Company, 1943. Price, $4.00.

NEW EDITIONS

Biochemistry for Medical Students. By WILLIAM VEALE THORPE, M.A. (CANTAB.), PH.D. (LOND.), Reader in Chemical Physiology, University of Birmingham. Third ed. Pp. 476; 39 illus. Baltimore: The Williams & Wilkins Company, 1943. Price, $4.50.

An Introduction to Medical Mycology. By GEORGE M. LEWIS, M.D., Member of the American Dermatological Association, Inc.; Fellow of the American College of Physicians, of the American Medical Association and of the New York Academy of Medicine; Member of the New York Dermatological Society and of the Manhattan Dermatological Society; Associate Attending Physician (Dermatology), The New York Hospital; Assistant Professor of Clinical Medicine (Dermatology), Cornell University Medical School; Attending Dermatologist to St. Clare's Hospital; Visiting Dermatologist to Welfare Hospital, etc.; and MARY E. HOPPER, M.S., Research Fellow in Medicine, Cornell University Medical School. Second ed. Pp. 342; 77 plates (1 in color). Chicago: The Year Book Publishers, Inc., 1943. Price, $6.50.

The Compleat Pediatrician. By W. C. Davison, Professor of Pediatrics, Duke
   University School of Medicine, Formerly Acting Pediatrician in Charge,
   The Johns Hopkins Hospital. Fourth ed. Durham, N. C.: Printed by
   Seeman Printery for Duke University Press, 1943. Price, $3.75 by check
   or $4.00 on credit.

Physiology of the Nervous System. By John Farquhar Fulton, M.A.,
   D.Phil., D.Sc. (Oxon.), S.B., M.D. (Harv.), Sterling Professor of Physiol-
   ogy, Yale University, Formerly Fellow of Magdalen College, Oxford.
   Second ed. Pp. 614; 111 figs. London, New York, Toronto: Oxford Uni-
   versity Press, 1943. Price, $9.00.

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ORIGINAL ARTICLES

GRADENIGO SYNDROME COMPLICATED BY PNEUMOCOCCIC MENINGITIS; RECOVERY AFTER INTENSIVE TREATMENT WITH PENICILLIN AND SULFADIAZINE

By Lewellys F. Barker, M.D.[*]

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Though the Gradenigo syndrome (otitis media with head pains and paralysis of the 6th nerve on the same side) is less rare than was formerly thought, the case reported here is of especial interest because of the pneumococcic meningitis that developed and the favorable outcome under intensive treatment with penicillin and sulfadiazine.

Case History. The patient, a white woman, aged 35, an inspector in a manufacturing plant, entered the medical service of the Johns Hopkins Hospital on January 8, 1943, in a state of coma.

Family History. Has no bearing on the case.

Previous History. Aside from the ordinary diseases of childhood the patient has had fairly good general health. She suffered from several attacks of tonsillitis and 6 years ago had her tonsils and adenoids removed. She has had occasional headache and wears glasses for reading. Her habits have been good and she has worked steadily at her occupation until the present illness.

Present Illness. Two weeks before admission the patient developed a cold with sore throat and occasional stopping up of the ears. On January 2, on returning from work, the right ear ached. She developed general malaise and headache and was given drops to put into her ears by a local physician. At night she began to vomit, developed fever and had a chill. The next day she remained in bed but at night became delirious and her local physician finding a temperature of 105.5° F. gave her sulfathiazole, 1 gm. every 2 hours. Owing to persistent vomiting not much of the drug was retained and the medication was stopped. The vomiting persisted, the patient remained in a semidelirious state, and on January 6 was taken to the South Baltimore General Hospital. The temperature was then 105° F. and on account of the persistent delirium lumbar puncture was done and the cerebrospinal fluid was found to be cloudy and to contain 3300 cells, P.M.N. predominating. She was then sent to the Johns Hopkins Hospital for treatment of the meningitis and for further study.

Physical Examination on Admission. Temperature, 104.4° F.; pulse rate, 116; respiratory rate, 24; blood pressure: 120 systolic, 75 diastolic. Well-developed and well-nourished. Semicomatose but responds to painful stimuli. Skin dry. Face flushed. Breathing stertorous. Right eyelid swollen and red with yellow pus on conjunctiva. On moving the head the eyes remain fixed. Pupils small, equal, react to light. Right optic disk slightly hazy and veins

[*] Dr. Barker died July 13, 1943, a few months after submitting this manuscript.

rather full. Left optic disk normal. Right aural canal inflamed; drum injected and bulging. Pressure over the right mastoid causes pain. Purulent exudate in nose. Herpes on right cheek and on left upper lip. Heart and lungs negative. Abdomen negative. Bladder partially distended. Neck rigid on forward flexion and on rotation. Kernig sign bilaterally positive. Brudzinski positive. Other reflexes negative.

Laboratory Tests. Blood on admission showed a leukocytosis (white count, 20,200). Urine contained albumin on admission but soon became normal.

An ear, nose and throat consultant found pus draining from sphenoids, ethmoids and both antra.

Examination of the spinal fluid sent from the South Baltimore General Hospital revealed pneumococci within the pus cells.

On the following day there was complete paralysis of the right nervus abducens and beginning paralysis of the right nervus facialis.

Diagnosis. Purulent sinusitis with extension along the right Eustachian tube to the ear causing right otitis media, right mastoiditis and right petrositis with the development of pneumococcus meningitis and paralysis of the 6th and 7th cerebral nerves.

Treatment and Further Course. At 1.30 A.M. on January 7, 20,000 units of sodium penicillin (Florey) were given intravenously. At 2.15 A.M. lumbar puncture was repeated, 3040 white cells found, 94% polymorphonuclears, and 5000 units of penicillin were given intrathecally.

The culture that had been made on the preceding day from the spinal fluid showed a pure growth of pneumococci, Type 25, and a blood culture made on January 7 also revealed Type 25 pneumococcus.

At 3.30 A.M. on January 7, 15,000 more units of penicillin were given intravenously. Roentgen ray of the skull made on this day showed no evidence of destruction within the mastoid, but at 4.30 A.M., 1500 cc. salt solution and 500 cc. of 5% glucose were given intravenously and myringotomy and simple mastoidectomy on the right were performed. The mastoid was found to be markedly infected and was necrotic.

At 6.00 A.M., ½ hour after the completion of the operation, 15,000 units of sodium penicillin were given intravenously and the same amount at 7.30 A.M. and at 9.30 A.M.

At noon on January 7, 6 gm. of sodium sulfadiazine were given intravenously along with 500 cc. of citrated blood. The patient continued to look gravely ill, the eyes were fixed and directed toward the left. Another lumbar puncture was done at 5.00 P.M. on that day. The white cell count in the cerebrospinal fluid had already decreased to 6400 and culture made from the fluid on this day and from the vein remained sterile. The sulfadiazine level in the blood on January 7 was 17.6 mg. per 100 cc. At 8 P.M. on that day 3 gm. of sodium sulfadiazine were given intravenously along with saline and 5% glucose solution. On January 8 at 1 P.M., 5000 units of sodium penicillin were given intrathecally and 2 gm. of sodium sulfadiazine along with 5% glucose and saline were given intravenously. The sulfadiazine level in the blood was 11.6 mg. per 100 cc. There was a lessening of the depth of the coma, complete 6th nerve paralysis on the right and some weakness of the right facial nerve. Facial herpes continued as did the rigidity of the neck and the positive Kernig sign.

At 11 P.M. on January 8, 5000 units of sodium penicillin were given intrathecally and 2 gm. of sodium sulfadiazine intravenously. An hour later, 5000 units of sodium penicillin were given intrathecally.

On January 9, the white count in the cerebrospinal fluid was 7480; 5000 units of sodium penicillin were given intrathecally.

The patient began to improve rapidly, the temperature fell, she recognized people and talked with them but had occasional delirium. On this day a total of 8 gm. of sulfadiazine were given intravenously in divided doses.

On January 10, the temperature had become normal and the patient talked rationally. Six gm. of sodium sulfadiazine were given by clysis.

On January 11, 5000 units of sodium penicillin were given intrathecally and the sulfadiazine level in the blood was 6.2 mg. per 100 cc.

The right facial paralysis had become more marked and the paralysis of the right nervus abducens persisted.

On January 13, the patient complained of diplopia owing to the persistence of the right abducens paralysis.

Thereafter the patient continued to do well except for the persistence of paralysis of the nervus abducens and of the nervus facialis on the right. The penicillin and sulfadiazine were discontinued. It seems probable that the patient will recover later from the paralyses of the nerves.

Comment. The patient has been very fortunate in making such a good recovery from a pneumococcus meningitis. Until recently this disease has almost always proved fatal, though with the advent of the sulfonamide drugs many patients have recovered. In this case both penicillin and sulfadiazine were given in very large doses. In how far to attribute the recovery to penicillin, on the one hand, or to sulfadiazine on the other, or to both, is anyone's guess. Penicillin is known to have remarkable antibacterial powers against Gram-positive bacteria. Sulfadiazine is the safest of the sulfonamide drugs and it is unfortunate for the civilian population that temporarily the U. S. Army has had to take up so much of the supply that civilian hospitals for the present are asked to use other sulfonamide preparations as far as possible.

THE FEVER CURVE OF THERAPEUTIC FADS*

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It is, of course, all important that new therapies should be discovered, introduced into medical practice, and evaluated by actual use, for only in this way will the treatment of disease improve. However, it is unfortunate that almost every new therapy seems to have to suffer a similar fate at the hands of the medical profession. Each seems to have to run the gamut of overenthusiasm, disillusionment and neglect. Such a course of events appears at present to be inherent and inevitable.

One might draw a graph of the progress of a therapeutic fad just as one plots the fever curve of an infectious disease. The course of the graph will, in many instances, prove to be characteristic and recognizable, just as medical science has become familiar with the typical course of many fevers and can, from the fever curve, diagnose not only the morbid entity but the stage of the disease and sometimes deduce something of the prognosis.

Typhoid fever is the classical example of a disease with a characteristic fever curve, familiar, from extensive experience, to all but the youngest doctors. Three phases are recognized in the fever curve of typhoid—the stage of invasion with its daily rise to a higher evening

peak; secondly, the high maintained fever of the fully established disease, the fastigium; then when all goes well the fever commences to oscillate as the so-called amphibolic stage is reached. Finally, the falling curve of defervescence drops below normal for the first weeks of convalescence until all is restored to normal physiologic health.

When a newly recognized disease is defined it takes much study and many observations to enable us to know its typical course and symptoms. Once learned, however, we can make use of this information about the new just as we do in our old enemy typhoid fever. Could we perhaps think of a therapeutic fad as an epidemic infectious disease; could we by studying its course and behavior learn enough of its fever curve to diagnose it early, to recognize its state and even to prophesy its future? If we could do this we might be less readily swept away by each new fad; we might avoid the complications and dangers which are likely at the height of the fever; we might escape the later disappointment and remorse which should be the punishment for our loss of common sense and critical judgment. Although it may be stated parenthetically, such remorse does not seem to weigh very heavily on most of us; once the fad is dead, its evils are forgotten. This is fortunate for the physician's peace of mind but not for his scientific growth nor for his future patients.

An infectious disease picture is the result of interactions between the causative agent and the host. A therapeutic fad is equally so. There must occur a period of invasion after the introduction of a new therapy during which occur prodromata in the form of reactions of interest displayed by the host. After a varying period the actual onset of the fad takes place with rapid spread in the use of the new medicament and a feverish interest in it. Soon the disease is at its height. The symptoms, in a classical instance, include at this stage an unwarranted enthusiasm for the curative effects of the new drug or treatment, an extension of its use for all sorts and kinds of ailments quite foreign to the claims of the original discoverer. Soon a delirious euphoria develops which sees the new therapy as a panacea for all ills. At this stage, the mind and reasoning power of the profession seem to be obtunded.

One factor which raises the fever of the fad to even higher levels is the publication of reports of remarkable therapeutic results claimed for the method. Unfortunately, these reports are frequently hasty and ill-considered. The authors often are honest but deceived in their enthusiasm, attributing to the therapy of the moment benefits which may, in fact, be due to the psychotherapeutic influence of this same enthusiasm, or to associated items of treatment such as rest and diet. Where everything is being done for a patient, it is risky to give credit to any one procedure. One must be careful not to fall into the common error of "post hoc ergo propter hoc" reasoning. Improvement after a certain treatment does not always justify an assumption of therapeutic relationship.

Neither the fever of typhoid nor the frenzy of the fad ends by crisis. The maintained height of the curve is broken by increasingly sharp

falls with slowly returning consciousness and common sense. Reports of therapeutic failures and of toxic effects begin to appear. Criticisms of the method multiply until finally the good results obtained in certain cases are lost sight of and forgotten. It is not appreciated that the successes occurred only in properly selected cases, the failures in all others, for at this stage the criteria for proper selection are not clear. Unjustly, therefore, we turn against the method altogether, we forget its real value and discard it completely. The fever is now "broken," it is below normal and the disease is over. Convalescence is slow. After a kind of negative phase of complete inactivity, interest slowly returns through some reappraisal of evidence or improvement in method. And final restoration of health is reached when only a proper and judicious use is made of what was once a frenzied fad.

This may all sound fanciful and forced but the history of medicine records innumerable instances of therapies which have run just such a fever curve. And anyone who has lived some years in medicine has seen such incidents and has probably experienced it himself although it may be difficult for him to believe that he was ever so deluded. Let us choose a few examples.

Venesection is, of course, the most familiar example. Used without clear indications throughout the middle ages, its abuse came to a height with Benjamin Rush and the epidemics of yellow fever in Philadelphia toward the end of the 18th century. That any of his patients recovered amazes us today, as we read of the repeated large bleedings to which they were subjected.

When the pulse "acts with force" 10 to 20 ounces were removed; when the pulse was weak it was better to take only a few ounces at a time, repeating the process 3 or 4 times a day. But "if the state of the pulse be our guide, the continuance of its inflammatory action, after the loss of even 100 ounces of blood, indicates the necessity of more bleeding, as much as it did the first time a vein was opened."

And yet it all seemed so logical to Rush! As the blood settled in the bleeding bowl a buffy coat or, as it was called, "size" was formed. When this was thick it was sure evidence of noxious matter in the blood and, therefore, a clear indication for further bleeding. Today we know that this increased "size" of the blood was due to rapid sedimentation of the red cells as seen especially in infections, pregnancy and anemia. It was accordingly in infectious diseases and pregnancy that the fad of venesection rose to its greatest heights. Also it is obvious to us that the more one bled the more anemic the blood, the more rapid the sedimentation, the thicker the buffy coat and the clearer the indication for further bleeding. To quote Rush himself—"Bleeding should be repeated while the symptoms which first indicated it continue, should it be until four-fifths of the blood contained in the body are drawn away." What a logical but tragic vicious circle! It took a century before venesection recovered from these unwise excesses; the indications for venesection had to be reappraised before the method found its proper level of usefulness.

Benjamin Rush may seem so long ago that one may ask whether this century has seen any such therapeutic fads. The answer is a strong affirmative. For example, on the completion of my internship in 1910, I started to work in the Medical Outpatient Department of the University Hospital. My chief was an enthusiastic believer in the virtues of Thiosinamine. The fact that you have never heard of this drug does not alter the fact that in 1913 the Index Catalogue of the Library of the Surgeon General's Office, U. S. Army, recorded 76 articles and 4 books on the therapeutic uses of thiosinamine. It was believed to relax scar tissue wheresoever it might be; it was especially useful in stricture of the esophagus and in mitral stenosis. Many the case of rheumatic carditis I was made to listen to in order to record the improvement as the drug relaxed the stenotic mitral ring. As I think back to those days and develop my thesis in this essay, I almost find myself wondering whether there might not be some grain of value in this long neglected drug.

All the fads, however, have not been on the medical side of the house. The past half century has seen a number of surgical procedures, for what one might term neurasthenia, be introduced, rise to popularity and be abandoned as useless. Two of these, nephropexy and gastropexy, seemed at least to find some justification in the easily demonstrable ptotic position of the respective organs. Unfortunately, the logic that the nervous state was the result of the ptosis and would be benefited by restoring the fallen organ to its normal position was wholly fallacious.

The cart was far in front of the horse, for as we now know the primary trouble is the relaxed nervous tone of the patient and the ptosis of the abdominal viscera is but one manifestation of this, and certainly not the causative factor. Many have demonstrated that the position of the stomach in such individuals varies in both directions with the level of vasomotor and nervous tone. It is hard to believe in retrospect, how sure we all were of the good results of this useless surgery, and it is amazing how difficult it is to forget such useless knowledge as the technique of gastropexy which was much emphasized by prominent teachers to us medical students of those days. Of course, it is obvious that everyone was carried away by the apparent reasonableness of the procedure and was self-deceived by the not infrequent temporary benefits due in all probability to the psychotherapeutic effect of the operation. Any similarly spectacular treatment might have done as well. Like all such fads this one ran its course and was abandoned. But as always, another was ready to take its place.

One of the most virulent attacks from which the profession has suffered, not to mention the thousands of patients, was the fad of intestinal autointoxication. This was no single frenzy for it resulted in many secondary or complicating troubles. It again seemed so logical and reasonable; toxic matters must be formed in the gut, their absorption must obviously cause any or all symptoms. The degree and kind of this process could be estimated by the degree and exact tint of the

indican reaction in the urine—light or dark green, blue or bluish green. From this start, the fad followed obvious roads leading to the absurdities of "high colonics" carried out in cubicled offices resembling stables with many stalls. When this field began to fail, these cells were found equally convenient for the similar nonsense of duodenal lavage. The same honest but self-hypnotized physicians, often the same patients—the only change the tube and the orifice.

At least these results of the autointoxication theory were relatively harmless, but the fever had to rise to higher levels. If the colon was the site of this production and absorption of toxic matters, what more sensible than to remove the offending part? Incredible as it sounds today, this was advocated and done by not a few leaders of the profession, sometimes with a high operative mortality. This fad is now as dead as some of its victims. One may say that medical science must advance by trial and error—but in this case the error seems to have been on the inexcusable side.

Sometimes a therapy, medical or surgical, remains improperly thrown into the discard because at the time it is not possible to discover the correct indications for its use. In this situation is Edebohl's operation of decapsulation of the kidney. First introduced for so-called "nephralgia," it was later used more logically to relieve tension within the renal capsule in the hope of obtaining diuresis in cases of anuria and nephrosis. The results were occasionally spectacular, but far more often no benefit was obtained. It may yet be revived as a method of cutting the sympathetic nerve supply to the kidney in cases of hypertension.

In such a situation the probable explanation is that this particular operation should only be performed in one selected group of cases, which we as yet cannot distinguish from the larger group. This is what is happening today to the surgical treatment of hypertension. We have seen the therapy introduced, have read many glowing reports of cures and are now in the stage of being disillusioned by frequent failures. It looks today as if the therapy was about to be dropped by all but the die-hard enthusiasts. There is no doubt whatever that in a very few patients the method gives remarkable relief. But in which patients? How does one select them? It is not enough to say that they must be in condition to withstand the surgery, we must learn to divide the cases of hypertension into their different etiologic classifications. Then and then only, will we be in a position to select those who will respond to surgery. We cannot expect a surgical operation to cure all patients with what in the final analysis is only a symptom and one which results from more than one cause.

These are perhaps enough examples from the past—but it would be easy to mention others such as the tonsillectomy craze which at one time, not so long ago either, approached the violence of the Dancing Mania of the Middle Ages. Even today the now well-established indications for removal of tonsils are not always respected. Dental extractions are also finding their proper indications but the removal of

impacted molars, merely because they are impacted, or the patient anemic or neurasthenic, still goes on merrily. In all such situations the great need is a clarification of the therapeutic indications, the great danger that lacking such proper control of its use it will cause disappointment, be considered useless thus denying its help to the few whom it would benefit.

Was there really no virtue in strychnine in spite of the tons prescribed by honest physicians to the depressed, the asthenic and the convalescent? Does calomel deserve its present oblivion? Therapeutic nihilism comes from repeated disillusionment. To avoid this, we must try to diagnose our current fads, to recognize the misuse of new therapies in time to prevent the excesses which lead to disappointment and discard. Let us look at the therapies of today with a critical eye.

It is safe to assume that at almost any given moment the medical profession has just recovered from one fad, is suffering actively from another and that still a third is incubating. Can we possibly see ourselves sufficiently clearly to recognize these? What stage of the vitamin fad are we in today? It must certainly be at its height for it would seem impossible for more patients to take more vitamins than is the case now. We must be approaching the end of the fastigium and soon will see the fevered excesses cease and the use of vitamins tend to be neglected until placed on a reasonable basis.

Advertising of vitamins must also, it would seem, be at its apogee. Commercial advertising cannot be blamed for the therapeutic fads of the medical profession but it is surely a contributing factor, just as the delirium of fever will be more violent in those much addicted to alcohol. Let us not allow ourselves to become too subject to the influence of alcohol or of advertising, however honest, lest we reap the whirlwind in our next fever or fad. Advertising and alcohol are both excellent things within reason.

What of the sulfonamides? It seems inconceivable that any of our enthusiasm for these medicaments will ever be looked back on as a fad. The evidence is too conclusive, the logic is so sure. And yet were we not just as sure of our facts in the period when we cured meningeal infection with the formaldehyde given off in the spinal fluid by administered urotropin? Read the literature on the treatment of septicemia and puerperal sepsis by intravenous mercurochrome. The problem was solved and yet the method fell into disrepute long before sulfanilamide was available.

As usual we feel sure of our ground with regard to the sulfonamides. We believe we know something of the mechanism by which this series of substances act in bacterial infections and as usual everything is logical. But now we are being led to believe that the sulfonamides are equally curative in certain virus diseases. Does what we know of the viruses make it probable that the antibacterial mechanism of the sulfonamides would also be antiviral? If not, can it be that we are at the old game of deceiving ourselves—impossible, of course—as usual?

At any rate we must admit we are going too far in our administration of the sulfonamides. Fever is, for many, a sufficient indication for a trial of some sulfonamide, and yet the sulfonamides cause fever and we are off on a vicious circle not so different from that followed by Rush. Because sulfonamides act in some infections they are tried in all infections—especially today in the virus pneumonias to the discomfort of the patient and the waste of not too abundant sulfonamide.

We have reached the stage at which reports of toxic effects and therapeutic failures are appearing in the medical press. We need not here review the toxic manifestations but some are serious and even fatal, nor the causes for failure other than the sulfonamide-resistant strains of pneumococci and even gonococci. Warnings against the promiscuous use of sulfonamides are now appearing. It seems impossible, of course, that any of these factors should ever swing the pendulum to a neglect of the obvious value of these chemical drugs—yet let us not be too complacent—there is many a precedent for behavior almost as absurd.

We have touched on a few of the therapeutic fads of the past; we have cast a bilious eye on the fads of the present—but what new fad is incubating prepared to start us on some feverish episode? Perhaps it will be still another anti-bacterial derived from moulds, perhaps an almost instantaneous cure of syphilis or even of all venereal diseases, or shall we all be breathing triethylene glycol many hours a day—even wearing masks to enable us to do so when we are out in the dangerous fresh air. Prophecy is always difficult and, with regard to fads, impossible.

The most we can do is to be on the alert to recognize the next in its incipiency. We must diagnose it early from its characteristic symptoms and course.

We must keep a watch upon ourselves constantly lest we follow the same roads that we have before. We must be critical and even skeptical without losing our optimism or our openmindedness. We must scrutinize our therapeutic achievements to be certain they are surely due to the therapy we praise and not to insidious subtle psychotherapeutic effects unintended and unsuspected by ourselves. We must be sure our good results are not due to good associated care, diet and rest, or even to that very real force the "vis medicatrix naturae." If we are sure of the action of a therapy we must remember that it will be specific or of benefit, only in certain cases and we must not be led to try it in all. Let us try to judge matters for ourselves and not merely follow the herd blindly.

Finally, let us admit that we are human and have all the frailties of our predecessors and contemporaries in medicine. If we start with this premise we shall come more humbly to a self-correcting realization of our own lack of resistance to therapeutic fads. None of us is immune—but if we can recognize the danger we can perhaps avoid the contagion.

THE DETRIMENTAL EFFECT OF FREQUENT TRANSFUSIONS IN THE TREATMENT OF A PATIENT WITH HEMOPHILIA

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MANY agents have been recommended for the treatment of hemophilia, but with one exception they have not stood the test of time. This exception is transfusion of blood. Most discussions of the treatment of hemophilia agree that a transfusion of normal blood, plasma, or fractions prepared from plasma[2-6] results in a definite though transient improvement in the condition, usually lasting 2 to 6 days.

Until recently the technique of blood transfusion was sufficiently complicated to restrict its use in hemophilia to acute manifestations of the disease. The availability of this form of therapy has greatly increased in the past few years because of the development of blood banks. It has, therefore, become feasible to use transfusions as a therapeutic agent much more frequently, without restricting their use to emergencies as previously.

So far there has been no indication that the use of frequent transfusions in treating hemophiliacs is contraindicated in any way. Observations which we have made on one case of hemophilia indicate, however, that both from a clinical standpoint, and from the aspect of clotting time, repeated transfusions of either whole blood or plasma lose their effectiveness in alleviating the condition, and even possibly have a detrimental effect. These observations extend over a period of about 4 years during which the patient received at least 3000 cc. of whole blood and 5000 cc. of plasma. The plasma used was in various forms, either prepared from freshly drawn blood, from 4-day old bank blood, or from lyophilized plasma restored to its original volume. During the latter part of this period detailed records were kept on the blood coagulation time and clinical condition of the patient, but for the earlier part detailed records are missing.

The patient under discussion is a hemophiliac, aged 36, with a family history of the maternal grandfather and second cousin both manifesting the disease. His history follows the usual course of hemophilia in a moderately severe form. He has had hemorrhages into various joints with resulting ankylosis of both elbows, the left knee and the right ankle. On frequent occasions since the age of 18 he has had hematuria due to hemorrhages originating in the kidneys.

The period covered by this report commenced in August, 1939, when he was admitted to the hospital due to a hemorrhage in the left thigh compressing the sciatic nerve. At this same time a severe hema-

turia developed and a transfusion of 500 cc. of citrated blood was given. This failed to stop the hematuria and was followed by transfusions on 3 successive days of .50 cc. of plasma. Following this the hematuria stopped.

At that time it was decided to obtain a quantity of normal plasma and preserve it in the lyophile state for therapeutic use. Approximately 450 cc. of plasma were lyophilized in 25 cc. lots. As the need arose, indicated by the appearance of hemorrhages, 1 or 2 of the vacuoles were restored to the original volume and injected intravenously. During the year that this supply of dried plasma was available it was given on the average of once a month. While no record of blood coagulation times were kept, it was observed that the plasma initially had beneficial effects, but that later its effectiveness decreased.

After the supply of lyophile plasma was exhausted, no transfusions of any kind were given for a period of about 6 months. At this time (March, 1941) the patient's clinical condition became very poor and the plasma from about 75 cc. of fresh blood was given. A marked improvement resulted and the patient was free from hemorrhagic symptoms for a period of about 3 weeks. The beneficial effect was so marked that on the reappearance of hemorrhages another transfusion of fresh plasma was given; this time, however, no improvement of his condition occurred. Further attempts to ameliorate his condition by transfusions of 50 to 100 cc. of fresh plasma given at intervals of 2 to 3 weeks also produced no result.

In August, 1941, the patient came under our care, and it was decided to conduct a further study of the effect of transfusions on his condition. The record of the transfusions given is shown in Table 1 together with the clotting times of venous blood taken before and after the transfusions. Since the patient's red blood cell level was usually normal, in some cases 500 cc. of blood were withdrawn before giving the transfusion. As shown in the table, none of these transfusions had any effect on the clotting time with the exception of those given on 9–10–41 and 11–28–42. It is also noteworthy that the clotting time has had a tendency to increase during this period. Clinically, the condition of this patient has become somewhat worse. It has been noted particularly that while he previously had severe phases alternating with periods of relative remission, he now appears to be in a continuous severe phase which has persisted for about a year.

Discussion. The observations presented here indicate that in one hemophiliac who has received numerous transfusions during the past 3 years the beneficial effect of transfusions has become questionable and even suggest that they may have become detrimental. We feel that in view of these observations, care should be taken in treating hemophiliacs by transfusions, and that they probably should not be given them as a prophylactic measure but, rather, that the measure be reserved to cope with emergencies. Johnson[3] has reported on the successful prophylactic treatment of two hemophiliacs by transfusion of lyophile plasma over periods of 3 and 5 months respectively. This, however, is not comparable to the period of 3 years during which this

patient has been treated, and it may well be that with continued treatment his patients will also develop a refractory phase.

TABLE 1.—RECORD OF TRANSFUSIONS AND CLOTTING TIMES

Date 1941	Transfusions		Blood removed (cc.)	Clotting time of venous blood			
	Whole blood (cc.)	Plasma (cc.)		Before transfusion		After transfusion	
				Hr.	Min.	Hr.	Min.
8–14	..	250	..	3	45	1	00
8–26	..	250					
8–27	..	250	..	..	..	2	50
8–28	..	200	..	..	..	3	25
9–10	..	250	..	3	00	0	30
9–11	..	250	500	2	00	2	30
9–23	..	300	500	2	50	1	35
9–26	..	200					
9–30	..	350	500	3	30	2	30
10– 3	..	300	..	3	30	2	20
10– 8	500						
11– 3	120	..	..	2	30	2	00
12–30	..	..	500				
1942							
1– 8	..	..	..	2	15		
3–11	500	..	..	4	45	3	20
3–13	500	..	500	8	30		
3–20	..	250					
3–25	500	..	..	7+	..	4+	
6– 4	..	..	500				
7–20	..	..	500				
7–21	..	250					
8–14	..	200					
9– 5	..	275					
10–22	..	..	500				
11–21	500	..	500				
11–28	..	300	..	4	00	0	40
12–24	..	300					
1943							
2– 1	..	300	..	6	00	5	30
2– 3	..	300	..	5	00	4	30

Certain *in vitro* experiments, which were made with this patient's blood during this refractory phase, suggest a possible explanation as to its cause. It is commonly accepted that the addition *in vitro* of a small quantity of normal blood to hemophilic blood produces a normal clotting.[1,2,5] Previous to the period discussed in this paper it had been frequently observed that this was the case in respect to the blood of this patient. In 1941, following the series of 8 plasma transfusions totaling 1800 cc., this phenomenon was studied again on this patient, using plasma from oxalated blood and determining the clotting time of various mixtures of normal and hemophilic plasma after recalcifying. It was found that instead of the normal plasma causing clotting of the hemophilic plasma, the hemophilic plasma had acquired the property of markedly retarding the clotting of normal plasma. This was found to be the case at various times during the period over which transfusions were given. The clotting times of various mixtures at different times during this period are shown in Table 2. These data show that at this period the hemophilic blood contained a constituent which was inhibitory to the normal clotting process.

TABLE 2.—THE CLOTTING TIME OF MIXTURES OF NORMAL AND HEMOPHILIC PLASMA
AFTER RECALCIFICATION WITH 0.1 CC. OF 0.5% CALCIUM CHLORIDE

Hemophilic plasma (cc.)	Normal plasma (cc.)	Clotting time at dates shown									
		10-10-41		10-11-41		10-14-41		11-3-41		1-8-42	
		Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.	Hr.	Min.
0.5	0.0	2+	..	2+	..	3+	..	1+	..	2+	
0.4	0.1	2+	..	..	55	..	50	..	45		
0.3	0.2	2+	..	..	50	..	45	..	45		
0.2	0.3	1	50	..	50	..	30	..	45		
0.1	0.4	..	45	..	17	..	14	..	20	..	45
0.0	0.5	..	3	..	4	..	3	..	3	..	3

This constituent may be the antithromboplastin reported by Tocantins[7] to be the cause of the prolonged clotting time in hemophilia. It is possible that transfusion of normal blood, by supplying an increased amount of thromboplastin to the hemophiliac, reduces the amount of circulating antithromboplastin and thereby causes a temporary improvement. Subsequently, however, the antithromboplastin returns not only to its previous level but to one higher than existed before the transfusion. As a result of this a second transfusion has less effect than the first. With time, the abnormally elevated antithromboplastin returns to its initial level and at this point a transfusion again becomes effective.

Summary. The failure of repeated transfusions of blood and plasma to produce any improvement in the condition of a hemophiliac is described and a possible explanation offered.

REFERENCES

1. FRANK, E., and HARTMANN, E.: Klin. Wchnschr., 6, 435, 1927.
2. HOWELL, W. H.: Bull. New York Acad. Med., 15, 3, 1939.
3. JOHNSON, J. B.: J. Am. Med. Assn., 118, 799, 1942.
4. JONES, H. W., and TOCANTINS, L. M.: J. Am. Med. Assn., 103, 1671, 1934.
5. PATEK, A. J., and STETSON, R. P.: J. Clin. Invest., 15, 531, 1936.
6. PATEK, A. J., and TAYLOR, F. H. L.: J. Clin. Invest., 16, 113, 1937.
7. TOCANTINS, L. M.: Federation Proceedings, 1, 85, 1942.

THE TREATMENT OF AGRANULOCYTOSIS WITH SULFADIAZINE

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SINCE the introduction of prontosil and each of the subsequent "sulfa" drugs, much emphasis has been placed upon their possible toxic effects on bone marrow with development of agranulocytosis in susceptible individuals. Many authors have emphasized the necessity of discontinuing the drug immediately when blood counts in a patient receiving any sulfonamide show evidence of leukopenia. Some have observed only a transient leukopenia in patients receiving sulfonamides

with the white counts returning to normal levels despite the fact that the drug was continued.

The occurrence of agranulocytosis following the administration of drugs, especially amidopyrine and the benzamine group, has been known for some years. Since the introduction of prontosil many cases are on record in which each one of the sulfonamide group of drugs has been the etiologic factor in the development of this condition. Sulfanilamide and sulfapyridine have been the most frequent offenders, while relatively few instances have been reported in which agranulocytosis has been due to sulfathiazole[2,11,12] or sulfadiazine.[3,6]

Some patients with agranulocytosis recover spontaneously. In the fatal cases death probably is due to an overwhelming infection resulting from the absence of neutrophils and the loss of the body's normal defensive mechanism, the oropharyngeal ulceration and sepsis being only terminal phenomena.

The treatment of agranulocytosis, whether due to a drug, toxin or infection, has been unsatisfactory. Transfusions, liver extract, pentose nucleotides, etc., have had little effect in changing the usually fatal outcome of the disease. When agranulocytosis has occurred in the course of an infection treated with one of the sulfonamides the first thought, based upon the cumulative warnings published since the introduction of prontosil, is to discontinue the sulfonamide and to hope for spontaneous recovery following the usual treatment. However, it has been noted that the depression of white counts in some patients receiving sulfonamides may be only temporary, with an early return to normal levels even though the drug is continued. Further, the sulfonamides, especially sulfathiazole and sulfadiazine, have been used with beneficial results in the treatment of miscellaneous infectious processes with an associated leukopenia, and in some patients with agranulocytosis.[4,8,10] The bacteriostatic effect of these drugs apparently is independent of the granulocytes and may be just as effective in a patient with leukopenia or agranulocytosis as in one with a marked leukocytosis. Thus, in an individual without demonstrable granulocytes and with an overwhelming sepsis likely to cause death, the use of sulfonamides to combat the bacteremia seems logical if the maturation arrest due to previous sulfonamide administration is only a short-lived phenomenon. Successful treatment or prevention of the sepsis may tide the patient over the period of temporary bone marrow depression until the return of his normal granulocyte defenses.

We are presenting 3 cases of agranulocytosis in which we believe the successful outcome in each instance was due to the administration of large amounts of sulfadiazine.

Case Reports. CASE 1. A. L. H., a 26 year old, single, aviation cadet, was admitted to the hospital on October 24, 1942, complaining of chills, fever, and malaise of approximately 48 hours duration. The past history was negative except for the occurrence of measles, mumps and pertussis in childhood. On entry, examination showed the following: height, 65½ inches; weight, 145 pounds; temperature, 102.8° F.; pulse, 96 and respirations, 22. There was moderate redness of the pharynx with some associated cervical lymphadenopathy. The chest was clear. There was no rash. The remainder of the

physical examination was normal. The urine was negative. The white blood cell count was 13,300 with 75% segmented polymorphonuclear leukocytes, 5% juvenile forms, 17% lymphocytes, 2% monocytes and 1% basophils. Culture of the throat produced a hemolytic streptococcus, Lancefield type A, sub-group 12 (Griffith). The admitting diagnosis was nasopharyngitis though the possibility of early scarlet fever was considered likely. A mild scarlet fever epidemic was prevalent at the time. Forty-eight hours after admission the patient developed a strawberry tongue and a fine, punctate, erythematous rash typical of scarlet fever. On the fourth hospital day fine râles, with associated decreased intensity of the breath sounds, were heard over the right middle lobe. There was gradual fall of the temperature to normal by the 6th day and his chest was clear. Sulfadiazine had been started on admission, 1 gm. 6 times daily for 2 days then 4 times daily thereafter. From the 7th until the 11th hospital day the patient felt fairly well, remained afebrile, and the rash faded. The leukocyte count dropped to 6400 (43% polymorphonuclear leukocytes) on the second afebrile (8th hospital) day.

On November 3rd (11th hospital day) there was a recurrence of fever (101.2° F.) with associated reappearance of the scarlatiniform rash together with the return of a few râles over his right middle lobe. We considered this episode as a recrudescence of scarlet fever, rather than a reinfection, since the same type and strain of streptococcus was cultured from every other scarlet fever patient on the ward at that time. The W.B.C. count on the day of this recurrence had risen to 6800 (67% polymorphonuclear leukocytes).
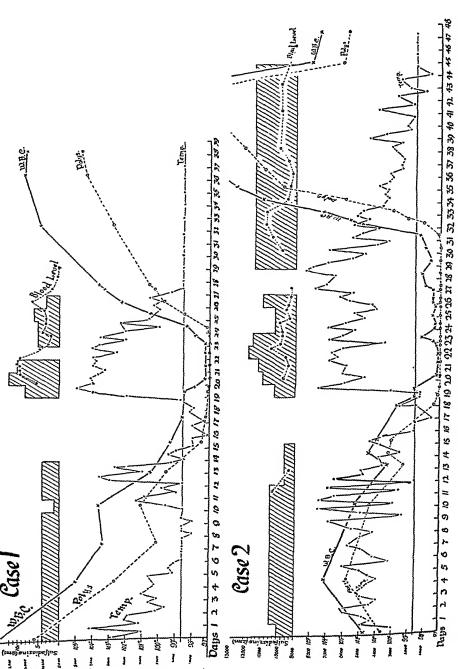
During the next 4 days there was an irregular temperature elevation to 103.2° F. and a return of sore throat. The temperature was normal on November 7 (15th hospital day) and the patient again felt fairly well. The W.B.C. count, however, had dropped to 3550 (72% polymorphonuclear leukocytes) on November 6. Sulfadiazine was discontinued after a total of 58 gm. had been given. On the 16th hospital day there was a further drop in the count to 2300 (23% polymorphonuclear leukocytes). Twenty-four hours later the count had reached 1600 (13% polymorphonuclear leukocytes). By this time the rash had faded, desquamation had occurred, and the lung was clear of râles. The administration of liver extract, 2 cc., and pentnucleotide, 10 cc., intramuscularly twice daily was started. The daily administration of 200 mg. of cevitamic acid intravenously was begun. These measures were with no apparent effect since there was a continued fall in the count of all of the white blood cell elements.

By November 11 (18th hospital day) the W.B.C. count totaled 2250 and no polymorphonuclear leukocytes could be found in the many smears examined. There was a sudden rise in temperature with reappearance of sore throat and cough productive of mucopurulent sputum. On that day 250 cc. of citrated whole blood was given. On the next day, November 12, the patient's condition was worse, his temperature ranged from 103° to 105° F. and it was apparent that he probably would not survive. Believing that death from overwhelming infection would probably occur and surmising that possibly the agranulocytosis might be consequent to the effects of the hemolytic streptococcus and not to the drug, it was reasoned that if infection could be held in abeyance long enough, the bone marrow would recover and the patient might be given a chance for survival. Accordingly, the use of liver extract, pentnucleotide, cevitamic acid and transfusions, was abandoned. Sodium sulfadiazine was given intravenously twice daily in amounts sufficient to raise the blood level to 20 to 25 mg. per 100 cc. At the same time the use of convalescent scarlet fever human serum was begun. This was given in doses of 100 cc. daily for the next 11 days.

During the first 3 days (19th, 20th and 21st hospital days) of treatment with sodium sulfadiazine and serum the patient remained in a critical condition, his temperature was held at 103° F. or higher, and he developed ulcerations of the mucous membranes in the faucial regions and at the anus. By November 15 (22d hospital day), after 3 days of such treatment, icterus appeared, the R.B.C. count dropped from 5.1 million to 3.75 million with the hemoglobin
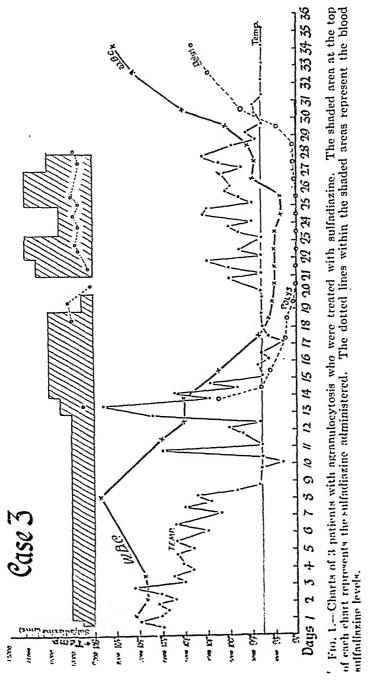
falling from 16.4 to 11.8 gm. per 100 cc. In an effort to halt the progrses of
hemolysis sulfadiazine was discontinued for 1 day (November 15) to allow the
sulfadiazine to fall to a lower blood concentration. Resumption of the drug on
November 16 maintained the blood level between 5 and 10 mg. per 100 cc.
From November 12 to 15 the total W.B.C. count varied from 200 to 310, all
lymphocytes. No polymorphonuclear leukocytes could be seen in any of the
smears examined. The first suggestion of recovery of the bone marrow did not

occur until November 17, after 5 days of complete absence of granulocytes, when the total count rose to 1470, and of 100 cells counted 98 were lymphocytes and 2 immature granulocytes.   Thereafter, there was a rapid rise in all of the W.B.C. elements so that by November 21 (28th hospital day), there was no evidence of any blood dyscrasia.

Coincidental with the signs of improvement in the blood picture, the temperature began to fall gradually, reaching normal on November 20, 9 days after the onset of the third febrile episode. Physical signs and Roentgen ray evidence of pneumonia involving the posterior aspect of the right lower lobe first appeared on November 17.   These signs cleared rapidly with the fall of the fever. Although sputum was by then rusty, no pneumococcus could be typed.   A hemolytic staphylococcus was recovered from the sputum and the throat lesions.

Fig. 1.—Charts of 3 patients with agranulocytosis who were treated with sulfadiazine. The shaded area at the top of each chart represents the sulfadiazine administered. The dotted lines within the shaded areas represent the blood sulfadiazine levels.

Except for a right inguinal adenitis which occurred as a complication of the anal ulceration, the hospital course subsequent to the return of the blood picture was uneventful. The patient, fully recovered, was discharged from the hospital on December 22, approximately 2 months following admission. Six weeks later (February 3, 1943) this patient again was hospitalized with an acute follicular tonsillitis of 2 days duration. A strain of hemolytic streptococcus was cultured from his throat. He had a normal response to sulfadiazine and was afebrile after 5 days. During this time 35 gm. of the drug were given. The patient ran the normal expected leukocytosis during the first few days of the infection and there was no demonstrable effect on the blood picture. He was discharged on February 14, fully recovered.

CASE 2.   K. H. K., a 24 year old aviation cadet, was admitted to the hospital on November 14, 1942 complaining of sore throat, dry cough, headache, and malaise of 2 days duration. The past history was not relevant. On admission the examination showed the following: height $71\frac{3}{4}$ inches; weight 185 pounds; temperature 101.4° F.; pulse 108; respirations 24 and blood pressure 110/70. There was moderate pharyngitis. The lung fields were clear. The remainder of the examination was normal. The urine was negative. The white blood cell count was 4700 with 70% segmented forms, 6% juvenile forms, 21% lymphocytes and 3% monocytes. The admitting diagnosis was nasopharyngitis. During the first 16 days of hospitalization the patient was only modertaely ill, his temperature ranging from 100° to 104° F. On the 3d hospital day signs of pneumonia involving the right lower lobe were evident. Because of the clinical course, the absence of any specific bacterial flora in the sputum, and the absence of leukocytosis, it was considered that the pneumonia was of the "virus" type. During this episode the patient received a total of 76 gm. of sulfadiazine. Other medications administered were potassium iodide, codein and aspirin.

From December 1 to 3 (17th to 19th hospital days) the patient was afebrile and felt improved. The Roentgen ray showed considerable clearing of the pneumonia. Whereas the white blood cell counts had ranged from 3550 to 5700, with a normal differential picture during this first febrile illness, there was a sudden drop to 2650 with 12% polymorphonuclear leukocytes on December 3. By the next day the count had dropped still further to 1300 with only 1% polymorphonuclear leukocytes. At the same time the temperature abruptly rose to 104.6° F. and there were physical signs and Roentgen ray findings of pneumonia, this time in the right upper lobe. Soon thereafter the typical necrotic throat lesions, characteristic of agranulocytosis, appeared. From December 4 through December 12 (20th to 28th hospital days) the W.B.C. count ranged from 130 to 1050 cells per c.mm., all lymphocytes. Not a single polymorphonuclear leukocyte could be found during this time. On December 13, a few juvenile forms were observed and thereafter there was a rapid return of the blood picture to normal.

Because of our experience with Case 1 it was felt that resumption of the use of sulfadiazine might save this patient from overwhelming bacterial infection. Beginning December 4 (20th hospital day) the drug was given in a dosage sufficient to maintain the average blood concentration between 5 and 10 mg. per 100 cc. By December 11 (27th hospital day), after 8 days of such treatment, 64 gm. of the drug had been given. A new area of consolidation had appeared at the left base and the patient was still critically ill, having run an extremely stormy course with high fever. At that stage there was no evidence of return of the blood to normal, and the authors, being rather faint at heart, stopped the drug again. By December 13 (29th hospital day) the patient had been 2 days without sulfadiazine. Even though a few polymorphonuclear leukocytes were reported for the first time, the patient was worse. There was further spread of the pneumonia to the previously cleared right lower lobe, the temperature rose to 105.6° F., auricular fibrillation appeared and with it additional respiratory embarrassment due to congestive cardiac failure. The patient was comatose and deeply cyanotic and it seemed that he could survive for only a few more hours. Rapid digitalization and the use of oxygen con-

tributed some relief to the cardio-respiratory difficulties. Since discontinuance of sulfadiazine was considered a factor in the increased severity of the illness, its use was resumed for the third time in a dose of 10 gm. daily. With reinstitution of this treatment there was evidence of beginning recovery of the bone marrow as shown by the appearance of juvenile polymorphonuclear leukocytes in increasing numbers in the blood. By December 20 (36th hospital day and the 6th day of the third course of sulfadiazine), the count had risen to 14,150 with 85%. polymorphonuclear leukocytes. With the progressive rise of the count there was an associated fall in the fever and general improvement. By December 29 (45th hospital day) the patient was afebrile and sulfadiazine was discontinued. One hundred and fifty gm. of the drug had been given over a 15-day period during this third course of treatment; 290 gm. had been given throughout the entire hospital stay.

Because of the development of a moderately severe hemolytic anemia with fall of the hemoglobin level to 9 gm. per 100 cc. two whole blood transfusions of 500 cc. each were given on December 12 and 14. Donors who had recently recovered from "virus" pneumonia were used. In addition a total of 1800 cc. of human convalescent "virus" pneumonia serum was given in divided doses intravenously every 3d day from December 6 through December 20 (22d through 36th hospital days). Liver extract was given in 2 cc. doses intramuscularly daily from December 4 through December 10. Recovery, after return of the blood picture to normal, was uneventful. After 1 month his strength had returned, he had nearly regained his weight and there was no evidence of any blood dyscrasia.

CASE 3. A. J. B., a 22 year old aviation cadet of Mexican descent, was admitted to the hospital on December 9, 1942 complaining of headache, chilliness and dry cough of 4 hours duration. The past history was not relevant.

On admission the physical examination revealed the following: height, 68½ inches; weight, 160 pounds; temperature, 103° F.; pulse, 100; respirations, 22. There was a dry nasopharyngitis and paroxysms of cough were frequent. The lung fields were clear to auscultation. The remainder of the examination was normal. The urine was negative. The W.B.C. count was 7150 with 77% polymorphonuclear leukocytes, 22% lymphocytes, and 1% monocytes. The hemoglobin was 15.2 gm. per 100 cc. The Roentgen ray showed pneumonic infiltration in the lower left perihilar region and in the right lower lung field and "virus" pneumonia was diagnosed.

The patient was moderately ill with daily peaks of temperature to 102.6° to 104° F. for the first 8 hospital days. On December 18 to 19 (9th and 10th hospital days) there was no fever and the patient felt much better. However, on December 20 (11th hospital day) there was return of fever with the associated signs of spread of pneumonia to the lower portion of the left lung. This second febrile episode was more severe than the first, being accompanied by more prostration, severe cough, and cyanosis requiring the use of oxygen. The dosage of sulfadiazine, which had been administered since admission (4 gm. daily) was doubled. On December 24 (15th hospital day) the temperature abruptly returned to normal after a febrile period of 4 days.

Whereas the blood picture had been previously normal a drop of the W.B.C. count to 2500 with 56% polymorphonuclear leukocytes was first noted on December 23. By December 26 (17th hospital day) it had dropped to 1800 with only 22% polymorphonuclear cells. Sulfadiazine was discontinued on the next day, December 27, after a total of 86 gm. had been given. Thenceforth the W.B.C. counts ranged between 600 and 1750 (all lymphocytes with absolutely no polymorphonuclear leukocytes) until January 6, 10 days later, when the first sign of bone marrow recovery was evident in the abrupt rise in the W.B.C. to 2850 with 3% immature polymorphs. Thereafter the blood picture rapidly returned to normal. The count on January 11 (33d hospital day) was 7400 with 48% adult polymorphs, 4% young polymorphs, 46% lymphocytes, and 2% monocytes.

During the period of complete absence of polymorphonuclear leukocytes there was a daily temperature elevation to 100° to 101° F. This disappeared

on the return of the blood to normal. In spite of the blood changes the pneumonia progressively cleared at this time. No throat lesions developed although there was clinical evidence of a moderately severe catarrhal laryngitis. With the return of the W.B.C. count to normal, sulfadiazine was discontinued (January 5, the 27th hospital day) after 60 gm. had been given over a 7 day period and after a total of 146 gm. had been given during the entire hospital stay.

Recovery, after the return of the blood to normal, was uneventful..

Comment. In each of the 3 patients there are common factors. Sulfadiazine in total dosages varying from 52 to 72 gm., had been given over a fairly protracted period early in the course of each man's illness. At the time blood counts disclosed granulocytopenia each patient still revealed clinical evidence of infection. The lowering of the total white count with the complete absence of granulocytes in the peripheral blood, forewarned the stormy course that was to follow. In the first 2 patients especially, the infections extended to nearly overwhelming proportions. It seemed obvious that these young men would die unless the original infectious process and the later uncontrolled spread of infection were held in check during the period required for the temporary bone marrow depression to subside.

Since Case 1 failed to respond to the usually recommended treatment for agranulocytosis it was suggested that perhaps we were erroneous in assuming that the blood changes were due to the drug but that instead, the streptococcus toxin might be the etiologic agent. If this were correct, the drug might well be resumed, offering some hope of controlling the infection pending recovery of the bone marrow depression. Our knowledge at that time of only one case report[3] of agranulocytosis due to sulfadiazine added weight to this opinion and further influenced our decision to administer large amounts of sulfadiazine. We were further stimulated in carrying out our plan of treatment when we learned from Dr. Madeline Fallon of Los Angeles that she had used sulfonamides with apparent success in several children with agranulocytosis which, in her opinion, had been induced by infection. The patient's dramatic recovery was gratifying.

Our assumption that the strain of hemolytic streptococcus causing the scarlet fever in Case 1 also produced the agranulocytosis appeared erroneous when Cases 2 and 3 developed agranulocytosis during the course of pneumonic infections of virus etiology. The occurrence of agranulocytosis as the result of virus pneumonia or other virus infections has not been reported to our knowledge. On the other hand, sulfadiazine occasionally has caused agranulocytosis and each of our 3 cases received moderate doses of sulfadiazine for 2 or more weeks prior to the onset of bone marrow depression. We now are convinced that the drug was the responsible agent in producing agranulocytosis in each of our cases.

The remarkable response in these cases demonstrates that despite the primary rôle played by sulfadiazine in causing agranulocytosis, the bone marrow can recover from the temporary depression even with continued or subsequent administration of large amounts of the same drug. This approach to the treatment of agranulocytosis is unique in

view of the constant warnings in the literature to discontinue sulfonamides immediately upon the first evidence of an impending granulocytopenia.   Based upon our experience with this small but striking group of cases we believe that the patient who develops agranulocytosis, regardless of the etiology, should not be deprived of the most effective means of combating complicating sepsis but should be given one of the sulfonamides, preferably sulfadiazine, in amounts sufficient to maintain a blood level of approximately 10 to 20 mg. per 100 cc., until such time as the temporary bone marrow depression is overcome and the normal protective mechanisms are again functioning.   Sulfadiazine is recommended because, of all the sulfonamides, it is least apt to cause serious toxic reactions.[1,5,6,7,9,13]

Summary.   Three cases of severe agranulocytosis due to sulfadiazine were treated successfully with large doses of sulfadiazine.   The agranulocytosis occurred during the course of acute infections (scarlet fever in 1 case and primary atypical virus pneumonia in 2 cases).   Each patient had received moderate doses of sulfadiazine for 2 or more weeks prior to the onset of bone marrow depression.   Transfusions, pentose nucleotides and liver extract in Case 1 were without any demonstrable beneficial effect.   Convalescent human serum was used as an adjunct to the sulfadiazine therapy in each of the 3 patients while oxygen was administered in Cases 2 and 3.   Even though the infectious processes may have played a part, sulfadiazine probably was the primary factor in causing the agranulocytosis.   However, the subsequent administration of large amounts of the same drug seemed responsible for the ultimate recoveries.

Conclusions.   1. Cases of agranulocytosis due to sulfadiazine administration during acute infections may be aided by subsequent dosage with the same drug.*

2. Spontaneous regeneration of polymorphonuclear leukocytes by the depressed bone marrow can occur during the administration of large amounts of sulfadiazine even though this drug was responsible initially for the depression.

3. Sulfadiazine is effective in controlling sepsis which usually accompanies agranulocytosis.

* Another patient, M. J. B., developed granulocytopenia, but not complete agranulocytosis (lowest W.B.C. count was 1750 with 2% polymorphonuclear leukocytes, 1% eosinophils and 97% lymphocytes) 1 week after having received sulfadiazine (52 gm. in 12 days) for moderately severe scarlet fever.   Ten days after admission to the hospital this patient developed the enanthem, followed in 48 hours by the exanthem characteristic of measles.   The leukopenia which occurred at the time of his measles infection did not seem significant.   However, subsequent W.B.C. counts revealed a gradual lowering of both the total W.B.C. count and the granulocytes until the lowest level was attained on the 28th hospital day, 10 days after the disappearance of his measles rash and 15 days after discontinuing the sulfadiazine.   A mild throat infection was the only complication.   Sternal puncture revealed many immature granulocytes.   Because of the absence of significant fever (highest temperature 100.2° F.) and other evidence of sepsis, and because this patient did not develop complete agranulocytosis, we did not believe sulfadiazine was necessary.   His complete recovery with a normal W.B.C. count and differential (7000 W.B.C. with 53% polymorphonuclear leukocytes, 43% lymphocytes, 2% eosinophils and 2% basophils) 10 days later, emphasizes the fact that some patients with a temporary depression of the bone marrow will recover without specific therapy.   Only continued observation over long periods of time can definitely establish the

4. In spite of previous warnings to the contrary, the use of sulfadiazine may be advisable in the treatment of agranulocytosis, irrespective of the cause, if infection is either present or imminent.

REFERENCES

1. BILLINGS, F. T., JR., and WOOD, W. B., JR.: Bull. Johns Hopkins Hosp., **49**, 314, 1941.
2. CARROLL, G., and KAPPEL, L.: Urolog. and Cutan. Rev., **45**, 749, 1941.
3. CURRY, J. J.: J. Am. Med. Assn., **119**, 1502, 1941.
4. DAMESHEK, W., and WOLFSON, L. E.: AM. J. MED. SCI., **203**, 819, 1942.
5. DOWLING, H. F., HARTMAN, C. R., SUGAR, S. J., and FELDMAN, H. A.: J. Am. Med. Assn., **117**, 824, 1941.
6. FINLAND, M., PETERSON, O. L., and GOODWIN, R. A., JR.: Ann. Int. Med., **17**, 920, 1942.
7. FINLAND, M., STRAUSS, E., and PETERSON, O. L.: J. Am. Med. Assn., **116**, 2641, 1941.
8. FITZ-HUGH, T., JR.: Am. J. Clin. Path., **7**, 524, 1937.
9. FLIPPIN, H. F., ROSE, S. B., SCHWARTZ, L., and DOMM, A. H.: AM. J. MED. SCI., **201**, 585, 1941.
10. IVES, R. F.: Ann. Int. Med., **12**, 882, 1938.
11. KENNEDY, P. C., and FINLAND, M.: J. Am. Med. Assn., **116**, 295, 1941.
12. THOMPSON, L.: Northwest. Med., **41**, 133, 1942.
13. TREVETT, G. I., NELSON, R. A., and LONG, P. H.: Bull. Johns Hopkins Hosp., **49**, 303, 1941.

ACUTE TRAUMATIC HEART DISEASE

A CASE OF MYOCARDIAL CONTUSION WITH RECOVERY

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THE following case of acute traumatic heart disease seems worthy of reporting because of its rarity and because in this instance there is little likelihood of preëxisting heart disease.   This patient was observed early, and an essentially normal electrocardiogram was obtained at the onset.   A series of tracings was obtained which revealed serial changes that are pathognomonic of myocardial injury.   This may have been merely a cardiac muscle contusion, or, as seems less likely to us, this contusion progressed to a myocardial infarction.   There is little reason to believe that any degree of coronary artery occlusion occurred.

Case History.   V. B. T., a white aviation cadet of 22 years, was admitted to the Station Hospital, SAAAB (Reg. No. 3831 and 4004), August 15, 1942, complaining of pain over the lower portion of the sternum, dyspnea, and of constricting chest pain with radiation to the jaw.   These symptoms had been present and increasing in severity for 11 hours.   Twenty-four hours before entry he had received a blow over the lower sternum from the elbow of a fellow student while playing football.   This blow, as he described it, was strong enough to stun him and throw him to the ground, but in a few seconds he resumed play and his symptoms appeared approximately 12 hours later. Examination disclosed tenderness and edema over the lower portion of the sternum, but no evidence of fracture was obtained by Roentgen ray examination.

The family history was irrevelant; the past history gave no indications of congenital or of acquired heart disease. There had been no serious infections and there were no suggestions of the rheumatic syndrome. The usual aviation cadet health survey and physical examination had been made a few days prior to the accident and no gross abnormalities were found. The examination included Roentgen rays of the heart as well as strenuous functional tests.

Upon admission the patient was somewhat dyspneic and was more comfortable in the sitting position. The oral temperature was 99.6° F., pulse 110, respirations 20; the skin moist and warm. Forceful pulsations were noted in the blood-vessels of the neck. Blood pressure 140/75. He complained of pain radiating to the left side of the neck and jaw, and also to the tip of the left shoulder. This pain was made worse by deep inspiration and by movements of the trunk. The lower portion of the sternum, with its overlying edema, was exquisitely tender. In the left axilla there was decreased resonance and the breath sounds were partially suppressed. The area of cardiac dullness was considered to be somewhat increased and the heart sounds faint. The rhythm was regular. There was moderate epigastric rigidity, but no abnormal tenderness.

The initial Roentgen ray examinations seemed to be within normal limits. However, comparison at a later date with studies of his chest made at his initial examination for cadet training showed the cardiac outline to be larger than before. One day later a small amount of fluid at the left costophrenic angle was revealed by Roentgen ray; but this had decreased in amount by the third hospital day. The first electrocardiogram was normal, save for a suggestion of elevation of the RS–T segment in Lead II.

The fever reached a peak of 100.4° F. on the second hospital day, but he was afebrile after the third day. The local and general symptoms rapidly disappeared and the pleural fluid decreased. The blood pressure before discharge was 115/65. At this time it was considered that there might be a small amount of blood within the pericardium, but as the patient was free of symptoms and seemed quite well he was discharged August 21.

Two days later the patient was readmitted to the hospital in a semistuporous condition with dyspnea, cyanosis and orthopnea. A few hours before he had suddenly developed severe precordial pain which again radiated into the neck and also into the interscapular region. His initial dyspnea had been rapid in onset and most severe.

When examined there was evident respiratory distress, and numerous crepitant râles were present at both lung bases. The heart seemed normal in size, was rapid, hyperactive, and regular. Blood pressure 120/80. During the first few hours a loud, rough, to-and-fro murmur was heard over the base of the heart, the diastolic elements being louder, and best heard at the third intercostal space just to the right of the sternum. There was also a short, soft systolic murmur at the apex. These murmurs, apparently associated with acute cardiac decompensation, were intermittently audible over a period of about 12 hours. Under morphine the pain was controlled, and the pulse, which was always regular, dropped from 130 to 112; the respirations fell to 24 and the temperature to 99.4° F.

On the day following the second admission the heart was found to be further enlarged by Roentgen ray when compared with the previous examinations, and there was evident vascular congestion at both lung bases. Some fluid had reappeared at the left base.

No significant abnormalities were found upon laboratory examination of the blood or urine. Repeated determinations of the erythrocyte sedimentation rate were well within normal limits. Two blood cultures were sterile.

The remainder of the patient's course in the hospital was stormy and protracted, in that excitement and exertion brought on dyspnea, tachycardia, and early signs of decompensation. Recovery from each attack, however, was rapid. A 60 day furlough was granted on October 19, 1942, and during this period the patient was free of dyspnea and pain. He remained entirely comfortable, his strength returned and he was even able to attend dances. There

was a moderate increase in body weight. Occasionally momentary twinges of pain were felt in a spot 8 cm. below the left nipple, these always being associated with twisting the trunk or with stretching the left side of the body. This pain has never been related to exertion or emotion.

At examination December 19, 1942, the patient gave the appearance of normal health. Blood pressure 120/80. No cardiac abnormalities were made out upon auscultation. Roentgen ray examination revealed the heart size and shape to be just as it was before injury and the lungs were clear. Upon fluoroscopic examination the cardiac pulsations were of good quality and amplitude along the left border; there was a suggestion of slightly weaker pulsations at the right border. There were no pericardial or diaphragmatic adhesions.

1				
2				
3				
4F				
	3 days	10 days	15 days	127 days
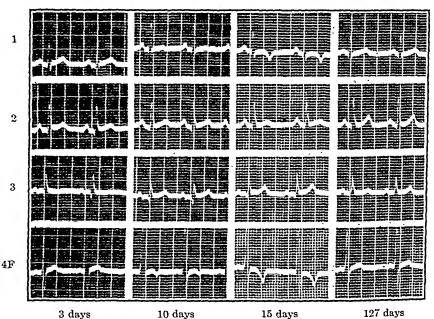
Fig. 1.—Serial electrocardiograms following a blow over the precordium of a healthy young man. Deep late inversion of T in Leads 1 and 4F is seen to reach a maximum at 15 days, with later return to normal configuration.

Reëxaminations of blood and urine were normal. The erythrocyte sedimentation rate was 2 mm. in 1 hour. The basal metabolic rate was +6%.

The EKG was normal, T4F now being upright, with further increases in the amplitude of the upright T2 and T3.

Discussion. Medical literature regarding acute traumatic heart disease is still confused. This is due, in part, to rapid change in terminology which has lead to inaccuracy in the use of terms. Thus, it is obvious that until very recently "coronary artery occlusion" and "myocardial infarction" have been used synonymously. Only in recent articles has there been indication that authors considered the possibility that coronary artery occlusion could occur without myocardial infarction; or conversely, that myocardial infarction could occur without acute coronary artery obstruction. A further difficulty is that most of the writing has been chiefly the reporting of case histories,

and these have been borrowed back and forth in a repetitious manner to such an extent that in reading papers one comes across the same history 5 or 6 times. Many of the case histories are inadequate and the associated comment frequently is irrelevant.

The standard textbooks on heart disease have little information regarding non-penetrating injuries of the chest producing heart damage. Stroud's recent textbook, however, has an excellent chapter by Hugh Barber.[1] White and Glendy[26] have contributed a chapter in Brahdy and Kahn's "Trauma and Disease" which contains an excellent general discussion and an adequate review of the literature. It is especially valuable for its critical review of the experimental literature upon traumatic cardiac disease. Warburg's monograph[24] published in 1938 is disappointing in that he has been more interested in the historical aspect of the problem and has merely compiled those instances of cardiac trauma already recorded in the world's literature. He does point out cases of traumatic heart damage which were reported in the latter part of the 17th century. Up to the beginning of the 20th century, 64 cases were on record. He finds 197 cases in the first 37 years of the 20th century. Fischer,[6a] in 1868, reported 452 cases of traumatic cardiac lesions, of which 76 were due to non-penetrating injury. Seven were considered to be cardiac contusions and 64 were cardiac ruptures. There was only 1 autopsy.

It is evident that even yet we have no satisfactory evidence regarding the incidence of cardiac contusion. It is usually thought to be very rare and the majority of the recorded cases have ended fatally. Experimental evidence indicates that most of the injuries should result in recovery. From this apparent discrepancy it is difficult to avoid the conclusion that the majority of the instances of cardiac contusion are not recognized. Thus, Stroud[22] is quoted as saying: "This subject is most important from the standpoint of insurance compensation; I still feel cardiac disease is unusual following anterior chest trauma." However, the same author, in editing a textbook on heart disease has included a long and well-written chapter on the subject. The point of view of its author is that cardiac contusion is of frequent occurrence. White[26] states that among 7600 autopsies at the Massachusetts General Hospital, which includes a busy accident service, there is not a single case of cardiac trauma on record as of March, 1936. Sanders[20] says that the combined records of the hospitals in Memphis contain no record of cardiac contusion, in a total of 326,500 admissions. Among these same admissions there were 10 penetrating wounds of the heart.

Excellent articles on the subject of cardiac contusion have been contributed by Beck,[2] Sigler,[21] Tuohy and Boman,[23] Kahn and Kahn,[8] and Leinoff.[9,10,11] The work of Bright and Beck[4] contains not only an adequate review, but their own experimental evidence.

Summary. 1. An instance of myocardial contusion with recovery is reported.

2. The symptoms, clinical course, and electrical deviations are similar to those of acute myocardial infarction.

REFERENCES

1. BARBER, H.: *in* Stroud's The Diagnosis and Treatment of Cardiovascular Disease, Philadelphia, F. A. Davis Company, Chap. XV, p. 268, 1940.
2. BECK, C. S.: J. Am. Med. Assn., **104**, 109, 1935.
3. BOAS, E. P.: J. Am. Med. Assn., **112**, 1887, 1939.
4. BRIGHT, E. F., and BECK, C. S.: Am. Heart J., **10**, 293, 1935.
5. Current Comment: Chest Injury and Coronary Occlusion, J. Am. Med. Assn., **119**, 1431, 1942.
6. DRESSLER, W.: Clinical Cardiology, New York, Paul B. Hoeber, Inc., p. 579, 1942.
6a.FISCHER, G.: Arch. f. klin. Chir., **9**, 571, 1868 (quoted by E. Warburg).
7. GLENDY, R. E., and WHITE, P. D.: Am. Heart J., **11**, 366, 1936.
8. KAHN, M. H., and KAHN, S.: Ann. Int. Med., **2**, 1013, 1929.
9. LEINOFF, H. D.: New York Med. Coll. and Flower Hosp. Bull., **1**, 246, 1938.
10. LEINOFF, H. D.: Ann. Int. Med., **14**, 653, 1940.
11. LEINOFF, H. D.: Arch. Int. Med., **70**, 33, 1942.
12. LEVINE, S. A.: Clinical Heart Disease, 2d ed., Philadelphia and London, W. B. Saunders Company, p. 255, 1940.
13. LEVINSON, L. A.: Ann. Int. Med., **1**, 227, 1927.
14. LEVY, R. L.: Diseases of the Coronary Arteries and Cardiac Pain (note by P. D. White, p. 276), New York, The Macmillan Company, 1936.
15. MASTER, A. M.: J. Am. Med. Assn., **113**, 440, 1939.
16. MASTER, A. M.: J. Am. Med. Assn., **120**, 392, 1942.
17. MASTER, A. M., DACK, S., and JAFFEE, H. L.: Indust. Med., **9**, 359, 1940.
18. MASTER, A. M., DACK, S., and JAFFEE, H. L.: Mod. Conc. Cardiovas. Dis., **10**, 11, 1941.
19. MASTER, A. M., GUBNER, R., DACK, S., and JAFFEE, H. L.: Arch. Int. Med., **67**, 647, 1941.
20. SANDERS, R. L.: J. Am. Med. Assn., **104**, 114, 1935.
21. SIGLER, L. H.: J. Am. Med. Assn., **119**, 855, 1942.
22. STROUD, W. D.: Editorial comment in Dick, G. F., and others: Year Book of General Medicine, Chicago, The Year Book Publishers, Inc., p. 699, 1940.
23. TUOHY, E. L., and BOMAN, P. G.: Ann. Int. Med., **4**, 1373, 1931.
24. WARBURG, E.: Subacute and Chronic Pericardial and Myocardial Lesions Due to Nonpenetrating Traumatic Injuries: A Clinical Study, New York, Oxford University Press, 1938.
25. WHITE, P. D.: Heart Disease, 1st ed., p. 439, 1931; 2d. ed., p. 390, 1937, New York, The Macmillan Company.
26. WHITE, P. D., and GLENDY, R. E.: *in* Brahdy, L., and Kahn, S., Trauma and Disease (2d ed., p. 26, 1941), Philadelphia, Lea & Febiger, p. 59, 1937.

A SOLITARY CALCIFIED CYST OF THE SPLEEN

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Two clinical entities should be thought of when the radiologist encounters a large annular calcification in the left upper abdomen. The first is a solitary calcified cyst of the spleen; the second, an aneurysm of the splenic artery. Solitary cysts of the spleen are not exceedingly rare;[11] calcified cysts are rare; aneurysm of the splenic artery is more common than one would think—at least 90 cases have been reported.[1,5,6]

Case Report. Miss B. M., white, female, aged 60, came to my office on December 29, 1941, complaining of itching eyelids. She had lost 28 pounds in the past 4 years and had a decided subicteric tinge. The pruritus was undoubtedly due to the jaundice. She had a second complaint of severe paroxysmal headache, usually localized to the left frontal region, rather typical of migraine, as it had been present over a long period of years.

Two years before, a lesion of the gall bladder had been reported after Roent-

gen ray examination.   (The calcified ring in the splenic region is said to have been absent at that time.)   Now in 1941 fullness was found in the left upper quadrant, with the definite suggestion of a mass on deep inspiration.   Physical examination was otherwise negative.   Her blood count on 12–30–41 was: hemoglobin, 61%; erythrocytes, 4,260,000; color index, 0.7+; leukocytes, 7400; neutrophils, 54% (segmented, 31% [young form, 1%]; non-segmented, 23%; lymphocytes, 39% [small]; 3% [large]; monocytes, 3%).   Her icterus index was 10.

In view of her previous history, the Graham test was repeated.   A large spherical mass with a calcified periphery was found lying in the left upper quadrant, suggesting a solitary cyst of the spleen (Fig. 1).   The left kidney had been displaced downward.   The right kidney was normal in size, shape and position.   The liver was normal in size.   There was no evidence of a renal, ureteral or vesical calculus.   The lumbar spine and pelvis were normal.   Two other possibilities were suggested; an old echinococcus cyst of the spleen; cyst of the left lobe of the liver.
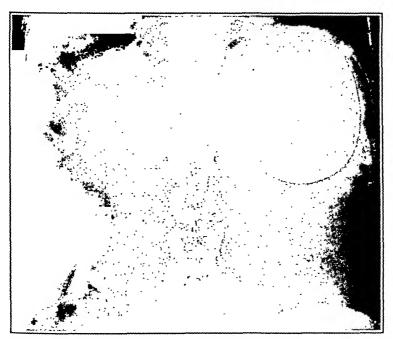
Fig. 1.—Large annular calcified shadow—left upper quadrant.   Preliminary film of abdomen (1–2–42).

Roentgen ray examination of the gall bladder by means of the Graham test showed that the gall bladder took the dye moderately well.   The shadow was homogeneous and there seemed to be an anatomic defect across the fundus Phrygian cap.   Following the fatty meal the gall bladder contracted about one-third.

Diagnosis.   Solitary calcified cyst of the spleen.   Normally functioning gall bladder—Phrygian cap.

To rule out the possibility of an echinococcus cyst an antigen was obtained and a scratch test made, which proved to be negative.

Laparotomy.   On February 16, 1942, a hard calcified tumor the size of a grapefruit, occupying the spleen, was delivered with difficulty.   The spleen and a small accessory spleen were removed.

Pathologic Report.   The spleen was stretched thinly (⅛ inch in thickness) over part of the surface of a cyst which was almost spherical and measured 12 x 13 cm. in diameter.   The surface of the spleen was smooth; of the cyst was shaggy.   The cyst projected from the region of the hilum displacing the

vessels 2 cm.   Its wall varied from 1 to 2 mm. in thickness, was rigid and calcified, with rough internal and external surfaces due to plaques of calcium.

FIG. 2.—Calcified cyst with the spleen lying over its distended surface.   (Incisions are for histologic sections.)
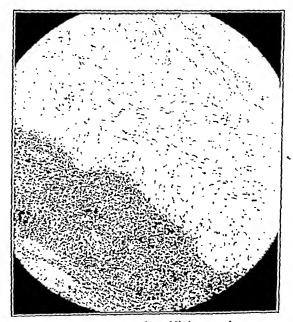
FIG. 3.—Histologic section of lining membrane.

The lining was smooth and contained 100 cc. of brownish turbid fluid with a glistening sheen suggesting cholesterol (Fig. 2).

Microscopic examination (Fig. 3) revealed a thick wall composed of collagenous fibrous tissue devoid of any epithelial lining. Plaques of calcified material were found. There was some lymphocytic infiltration in the laminated hyalinized fibrous tissue. The lymphoid tissue in the spleen itself was greatly decreased in amount. Numerous rather small vessels in one area suggest the possibility of hemangiomata, with rupture and hemorrhage as the possible cause of the pseudocyst.

Diagnosis. Solitary calcified cyst of the spleen.

Course. After 10 days of uneventful convalescence, the patient developed intense pain in the lower right chest with dyspnea and intense frontal headache. Her pulse became very rapid and weak. Her blood count on 3-3-42 revealed: hemoglobin, 55%; erythrocytes, 2,880,000; leukocytes, 4100; neutrophils, 70% (segmented, 67%; non-segmented, 3%); lymphocytes, 21%; monocytes, 7%; eosinophils, 2%. The prothrombin time was normal. Within the next 48 hours she developed a small area of thrombosis in the right superficial femoral vein and subsequently pain in the lower left chest. The chest condition was diagnosed as due to infarcts.

After splenectomy one expects the platelet count to rise, and embolism, thrombosis and infarction are the usual complications of this operation. We gave the patient heparin which prolonged her blood clotting time from 1½ minutes to 18 minutes. The blood platelets were 200,500 on 3-12-42, with a coagulation rate of 15 minutes. During her entire convalescence the leukocyte count never rose above 8250. The majority of the counts were around 4000. She made a slow recovery and is now perfectly well. No Howell-Jolly bodies were found, either before or after splenectomy.

Discussion. In the literature only 5 other cases of calcified cyst of the spleen could be found: Scotson,[9] Manchester, England (1933); Shawan[11] of Detroit (1937); Földes[4] of Germany (1927); Baumann and Kohnstamm[2] (1930); Culver, Becker and Koenig[3] (1942).

It is interesting to note the ages of the patients because one might expect calcification in the older age groups. Of these 6 patients the ages were 18, 25, 44, 49 (Földes[4]), 52 (Baumann and Kohnstamm[2]), 60 (my patient). Though other authors have stated that it was essentially a disease of females, 4 were females, 2 males.

The failure to find Howell-Jolly bodies after splenectomy is of interest in view of their occurrence, sometimes for many years (*cp.* O. H. P. Pepper's case[8a]); the finding is not constant in humans, however, and they are regularly absent in dogs after splenectomy.[8]

The position of the kidney on the affected side is interesting. In Shawan's[11] case the kidney was displaced upward. In my case it was displaced downward and was quite distinct and separate from the splenic shadow.

A very similar appearance is noted in calcified aneurysm of the splenic artery. The location is the same; the Roentgen ray appearance is the same. There is, however, one distinguishing clinical feature and that is a bruit. Pulsation may or may not be present in aneurysm.

There have appeared 2 reports of very similar cases in the *Journal of Radiology* while this paper was in preparation, 2 of which were aneurysms of the spleen,[10] and the third a calcified cyst of the spleen.[7]

From the surgical standpoint, operation on aneurysms of the splenic

artery is hazardous, with high mortality. It is not so hazardous on splenic cysts. It is important that the surgeon should know whether he is going to find an aneurysm of the splenic artery or a cyst of the spleen. Certainly the radiologist should advise the clinician of this possibility, and simple auscultation will readily make the differential diagnosis.

The purpose of writing this paper is to call the attention of the radiologist to the two possibilities which cannot be distinguished readily without listening for the bruit. Surgical intervention in aneurysm of the splenic artery is indicated. The mortality, however, is much higher than in solitary cyst of the spleen.

Roentgenologists will be interested in comparing the illustrations of this case with those presented in a case report by Montgomery[7] of a solitary cyst with a calcified wall in the *right* upper quadrant. We have little explanation for these cysts, but since they have been reported in children we must give considerable weight to the idea that they are fetal inclusions.

Summary. A calcified cyst of the spleen is reported, which it seems had probably developed since 1938. There is no record of its presence being observed in the films that were made at that time. Furthermore, the patient's itching and subicteric color were of recent origin, giving credence to the view that the cyst was of hemorrhagic origin and its calcification recent. We know that hematomas in muscle will calcify in 10 days so that there is no reason for us to postulate that this cyst was of congenital or juvenile origin.

Conclusion. The radiologist should be aware of two possibilities when annular calcified shadows are encountered in the left upper quadrant, namely, aneurysm of the splenic artery and calcified solitary cyst of the spleen. Second, the differential diagnosis can be made with the stethoscope. Third, aneurysm of the splenic artery and solitary cyst of the spleen are more common than the literature would indicate and should be given definite consideration in the presence of any left upper quadrant mass.

REFERENCES

1. ANDERSON, W., and GRAY, J.: Brit. J. Surg., **17**, 267, 1929.
2. BAUMANN, W., and KOHNSTAMM, O.: Rontgen-Praxis, 2, 26, 1930.
3. CULVER, G. J., BECKER, C., and KOENIG, E. C.: Radiology, **39**, 62, 1942.
4. FÖLDES, A.: Zentralbl. f. d. ges. Radiol., 3, 346, 1927.
5. GUY, C. C.: Surgery, 5, 602, 1939.
6. LOWER, W. E., and FARRELL, J. I.: Arch. Surg , **23**, 182, 1931.
7. MONTGOMERY, A. H.: Arch. Surg., **41**, 422, 1940.
8. PEARCE, R. M., KRUMBHAAR, E. B., and FRAZIER, C. H.: The Spleen and Anemia, Philadelphia, J. B. Lippincott Company, 1918.
   8a.PEPPER, O. H. P., and AUSTIN, J. H.: J. Am. Med. Assn., 122, 870, 1943.
9. SCOTSON, F. H.: Brit. Med. J., 1, 367, 1933.
10. SEIDS, J. V., and HAUSER, H.: Radiology, 36, 171, 1941.
11. SHAWAN, H. K.: Ann. Surg., 106, 469, 1937.
12. SHERWIN, B., BROWN, C. R., and LIBER, A. F.: Ann. Surg., 109, 615, 1939.

INTRAVASCULAR PARATHYROID GRAFTS

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The striking clinical pictures presented by the endocrine deficiency diseases are well known to all. Yet the field of "replacement surgery," as it was termed by Harvey Stone in a recent review,[10] is still one of the most challenging problems of modern therapeutics.

During the years 1906–1908 Halsted[4] performed many transplants of thyroid and parathyroid tissues in dogs, achieving considerable success in the iso-grafting of the latter into the preperitoneal tissues of dogs. In the course of these experiments he also formulated the concept that is often referred to as "Halsted's Law"—i. e., a physiologic need on the part of the host must be present if grafted tissue is to function. Recently some authorities have questioned the necessity of a preëxisting deficiency before grafting, Dunphy and Keeley[3] for example, having successfully iso-grafted adrenal tissue to the ovary of a dog whose other adrenal gland was still functioning. It has not been shown, however, that an animal with only one adrenal can be regarded as completely free of a deficiency.

On the basis of earlier work, Stone, Owings and Gey[11] in 1934 reported 2 cases of successful parathyroid cross-grafts in humans. From their experimental work on dogs, they had concluded that growing the tissue in the serum of the donor and the host as a preliminary to implantation was necessary before successful cross-grafts could be achieved. This method was also used by Houghton, Klassen and Curtis[5] in 1939 in a successful human parathyroid transplant. Over a period of 11 days, the graft was grown in a constantly changing media with an increasing proportion of the host's serum, and a decreasing proportion of the donor's serum. Both groups of workers used the axillary areolar tissue as the site of implantation.

In the past, other investigators had been attracted by more vascular organs such as spleen and kidney as logical beds for transplants. But because of this very vascularity and the postoperative formation of strangulating hematomata, they were forced to abandon these sites.

It appeared to us, however, that the fault lay primarily in the method of implantation rather than in the site selected, and that transportation of the grafts by the blood stream to the final bed might lessen the degree of postoperative hemorrhage. In 1933 Dinsmore,[2] in reviewing thyroid tumors and their intravascular metastases, gave excellent support for the efficacy of this method of grafting. Reid and Stevenson,[9] working at this clinic in 1936, attempted embolic grafting of

parathyroid glands to the leg muscles of dogs via the femoral artery. There were no clear-cut takes in these animals.

Stone, in the review already referred to, states that "the bed should be of loose structure, otherwise tissue pressure will compress the graft." As a method was at hand which enabled us to invade the most vascular organs, the lungs seemed to answer admirably this second prerequisite, that is, looseness of structure. With the foregoing as a basis, the following experiments were performed.

Method. Mongrel dogs were used. Through a midline incision in the neck, both thyroid glands were exposed. The inferior pole vessels were divided at least 2 cm. from the gland. Using these vessels as pedicles, the glands were separated from the surrounding muscle by sharp dissection. The lateral and upper pole arteries and veins were also divided as far as possible from the gland. The four parathyroid glands were dissected free from the mass of tissue and cut into 2 mm. size fragments, in all cases 4 glandules having been found. These were injected into the external jugular veins which had been previously isolated through the same midline incision. In several of the earliest experiments the glands were placed whole in the opened lumen of the vein. In all cases the transplants were flushed down toward the heart with 200 cc. of saline.

TABLE 1.—RECORD OF 11 PARATHYROID ISOGRAFTED DOGS SHOWING FREQUENCY OF ADMINISTRATION OF CALCIUM AND PARATHORMONE FOR THE TREATMENT OF TETANY

Dog No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	Remarks
668		x	x		x	x	x	x	x		x	x	x	0																	
573	x	x	x	x		x	x	x			x			x			x			0											
617			x		x			x		x				x								x								x	Sacrificed 6 months
566					x	x	x	x	x		x	x	x				x			x			x		x	0					
634					x	x		x		x		x																			Died 43 days
678								x			0																				
620				x	x	x				0																					
654	x										0																				
633															x			x									x	0			
621													Mild tetany on occasion—no therapy need																		Sacrificed 5 months
644				x	x	x				x				x	x				x		x						x			x	Sacrificed 7 months
Total daily therapy	3	4	2	7	3	5	6	3	4	4	3	4		2	2	1				1	2	2	1	1			1	1		2	

Postoperative days

Key: x, 10 cc. calcium gluconate and 1 cc. parathormone i.v.   0, dog died in tetany.

Results. Two groups of experiments were performed. Eleven dogs received their own parathyroid glands according to the procedure described above (Table 1). Three of these animals lived until sacrificed at 5, 6, and 7 months respectively after grafting; all had essentially normal blood chemical findings after having gone through a period in which calcium levels were sufficiently low to cause tetany. Eight dogs died of tetany when unobserved during the night (bitten tongues, upset food pans, and distorted positions being considered as evidence of a tetanic death). No deaths occurred during an observed attack of tetany, specific therapy being given when it became obvious that spontaneous recovery would not take place.

As shown on the accompanying chart, a composite of the records of these 11 animals, there was a marked diminution of specific therapy

needed to maintain them free of tetany during the second 2 postoperative weeks as compared with the first 2. It is important to note that the same number of dogs died in each period and that 3 dogs lived through both.

A second group of 12 dogs were operated on, cross-grafts of the parathyroids being performed according to the procedure described above. Five of these dogs lived for over a month postoperatively and one as long as 3 months. In general, these animals showed the same phenomenon, of decreasing frequency of specific therapy described above. However, after approximately 3 to 5 weeks there was again a
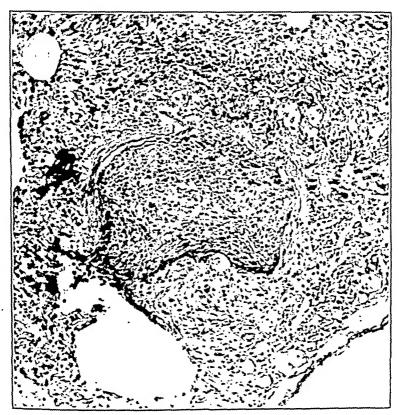
FIG. 1.—Photomicrograph of an embolus at the margin of the lung surrounded by an area of fibrosis. The tissue architecture is not characteristic, but the cellular detail closely resembles that seen in dog parathyroid. (× 150.)

rise in the frequency of therapy until, at the time of their deaths, they needed calcium and parathormone almost daily. Dog 700 can be cited as an example of this type of behavior, for after needing calcium gluconate and parathormone on the 6th and 9th postoperative days, he went 2½ weeks without therapy. On the 4th postoperative day the blood calcium level was 6.5 mg. per 100 cc. and the phosphorus 6 mg. per 100 cc.; on the 13th day, however, the calcium was 7.5 mg. per 100 cc. and the phosphorus 5 mg. per 100 cc. Yet from the 26th day until his death on the 53d day, he needed a total of 12 units of therapy, being given increasingly closer together towards the end of his life. Ten days

before his death in tetany, the calcium level was 5.2 mg. per 100 cc. and the phosphorus level 7 mg. per 100 cc.

There were no evidences in the immediate postoperative periods of the signs or symptoms of pulmonary emboli, or later of pulmonary infarcts. All dogs had careful postmortem examinations of the lungs, heart, and great vessels in an attempt to find the parathyroid emboli. A small mass in the left upper lobe of Dog 620, who died 2 weeks after cross-grafting, proved to be a fibrous tissue plug in a small pulmonary vessel. About the margins of this embolus are cells which microscopically resemble parathyroid cells. Sections of a similar mass in the lungs of Dog 617, sacrificed approximately 6 months after autografting (Fig. 1), showed it to be a cellular mass occluding a pulmonary vessel surrounded by a small area of pulmonary fibrosis. While the architecture of this tissue is not like that seen in normal dog parathyroid, the cellular detail resembles that seen in these glands.

Discussion.   In order to be certain that all parathyroids are removed it has been shown that it is necessary to perform complete thyro-parathyroidectomies. In 1931 Kunde, Oslund, and Kern[7] temporarily prevented the appearance of tetany in similarly prepared dogs by 75 to 100 gr. (8 to 12 gm.) of thyroid extract daily. Aub and co-workers[1] have demonstrated a definite augmentation of the effects of parathormone in tetany by the administration of thyroid substance. In our experiments we attempted, purely empirically, to establish a somewhat normal thyro-parathyroid relationship by the administration of 1 gr. (6.5 mg.) of thyroid each day. We do not believe this amount was sufficient to delay or prevent the appearance of tetany, nor were the animals myxedematous.

Considering the group of iso-grafted dogs, it appears to us that the phenomenon of decreasing need for therapy associated with a slowly rising calcium and falling phosphorus can be taken as evidence of functioning parathyroid grafts in the lungs. If it had been possible to give these animals 24-hour nursing care, we believe that many of the fatal attacks of tetany could have been aborted and more animals carried to complete recovery. This contention is supported by the fact that the 3 dogs that lived 5, 6 and 7 months on their transplanted glands, lived until sacrificed. Their records are very similar in the early postoperative weeks with those of dogs that died in unobserved attacks of tetany.

The course of the cross-grafted dogs is more difficult to interpret. Most of these animals appeared to be supporting growing grafts for some time when a change in their course occurred, finally ending in a tetanic death. This type of cycle is known to occur in cross skin grafts; and Stone, in discussing immediate cross-grafts of thyroid and parathyroid tissues, felt that involved in this phenomenon was a defense mechanism on the part of the host set in motion by the foreign protein of the graft.

When discussing the possible clinical application of this method of grafting, the effect of these small pulmonary emboli must be considered. In dogs, we can say that they did not give rise to any discernible

deleterious results.   Karsner and Ash[6] produced small areas of fibrosis in the lungs of dogs by the injection of turnip and radish seeds into the jugular vein.   They do not mention any ill effects suggestive of clinically significant emboli.   Norris and Landis,[8] in their textbook on diseases of the chest, mention that small pulmonary emboli pass unnoticed or cause at most "a few days disturbance."

The question of an adequate source of properly prepared and acclimated tissue for cross-grafting is beyond the scope of this report.   It is possible that stock tissue cultures grown in pooled human plasma might offer a satisfactory answer.   But given such a source, the method herein presented would lend itself to repeated grafting attempts until successful takes were achieved, repeated attempts with only a small degree of operative trauma and an unlimited implantation site.

Summary.   A method of achieving intravascular pulmonary grafts is discussed.   Experimental evidence in dogs is presented to demonstrate the efficacy of the procedure.

REFERENCES

1. Aub, J. C., Bauer, W., Health, C., and Ropes, M.:   J. Clin. Invest., 7, 97, 1929.
2. Dinsmore, R. S., and Hicken, N. E.:   South. Surg. Trans., 56, 12, 1933.
3. Dunphy, J. E., and Keeley, J. L.:   Surgery, 8, 105, 1940.
4. Halsted, W. S.:   Surgical Papers, Johns Hopkins Press, 2, 151, 1924.
5. Houghton, B. C., Klassen, K. P., Curtis, G. M.:   Ohio State Med. J., 35, 505, 1939.
6. Karsner, H. T., and Ash, J. E.:   J. Med. Res., 27, 205, 1912-13.
7. Kunde, M. M., Oslund, R., and Kern, R.:   Am. J. Physiol., 85, 387, 1928.
8. Norris, G., and Landis, H.:   Diseases of the Chest, Philadelphia, W. B. Saunders Company, 1940.
9. Reid and Stevenson: Unpublished data.
10. Stone, H. B.:   Ann. Surg., 115, 883, 1942.
11. Stone, H. B., Owings, J. C., and Gey, G. O.:   Am. J. Surg., 24, 386, 1934.

CARCINOMA OF THE DUODENUM

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From 1927 through 1939, 3 cases of primary duodenal carcinoma were seen at Pondville Hospital.   These rare tumors have received considerable discussion in the literature during the last 40 years. The situation is confused, however, by duplication of cases and by the inclusion of examples of carcinoma of the head of the pancreas, the papilla of Vater, the bile ducts, and the gall bladder.   Such errors have tended to increase the number of reported cases, particularly in regard to the second portion of the duodenum.   Many series of such cases must necessarily be set aside, and even after careful analysis, one cannot be absolutely certain that pancreatic carcinomas or other

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types of malignancies do not enter into the statistical recording. Since the major portion of the work may be devoted to the treatment of cancer, findings from Pondville and similar hospitals are not comparable with those from general hospitals. During the same period that the 3 duodenal carcinomas were seen at Pondville, there were 2 carcinomas of the papilla of Vater among a total of 1654 autopsies. In a similar period, there passed through the laboratory 181 carcinomas of the stomach and 444 carcinomas of the colon and rectum.

Deaver and Ravdin[8] and McGuire and Cornish[30] both reported an incidence of duodenal carcinoma of 0.03% in 151,201 collected autopsies and Eger[11] reported a similar figure in 350,286 collected autopsies. Table 1 shows an analysis of 117,433 autopsies with an incidence of 0.047% for carcinoma of the duodenum.

TABLE 1.—INCIDENCE OF DUODENAL CARCINOMA

Source	No. of autopsies	No. of duodenal carc.
Madyl,[26] Vienna, 1870–1881	20,480	2
Nothnagel,[38] Vienna, 1882–1893	21,358	5
M. Muller,[35] Berne, 1886–1891	5,621	6
Perry and Shaw,[40] Guy's Hosp., 1826–1893	17,652	4
McGlinn,[29] Phila. Gen. Hosp., 1913	9,000	1
Rupp,[45] Zurich, 1912	4,258	1
F. Muller,[34] Basle, 1874–1904	11,314	6
Nickerson and Williams,[37] Boston, 1896–1935	11,206	6
Meyer and Rosenberg,[33] Chicago, 1931	10,876	4
Jetter,[22] Buffalo, 1918–1937	5,668	0
Total	117,433	55 (0.047%)

In estimating the comparative incidence of carcinoma of the large and small bowel in the literature, a number of values are found: Raiford[44] 11.6%, Jefferson[21] 3.1%, Eger[11] 2.7%, Brill[4] and Ewing[13] 2.5%, Mayo[28] 1.4%. Analysis of 152 small intestinal carcinomas gives a percentage incidence of 1.47% (Table 2). What part other malignancies than carcinoma play in reported figures is hard to estimate. Medinger[32] reported 22 cases of malignancies in the small intestines with 30% sarcomas. Raiford[44] analyzed 88 tumors of

TABLE 2.—INCIDENCE OF CARCINOMA OF SMALL INTESTINE IN INTESTINAL CARCINOMA

Source	Carcinoma of small intestines	Total ca. intestines
Madyl[26]	6	100
Nothnagel[38]	11	243
M. Muller[35]	9	41
F. Muller[34]	8	123
Meyer and Rosenberg[33]	10	569
Raiford,[44] 1932	12	304
Nickerson and Williams[37]	8	343
Mayo Clinic,[28] 1907–1939	75	7,775
Stein,[52] 1931–1936	6	259
Jetter[22]	1	133
Pondville series, 1927–1939	6	450
Total	152 (1.47%)	10,340

the small intestines of which 38 were malignant, and 42% of those were carcinomata. If one correlates this fact with the published figures

of Jefferson, Eger, Brill, Ewing, and others, it will be seen that the value of 1.5% applies generally for the incidence of intestinal carcinomas in the small bowel. Including the stomach in the evaluation, the latest Mayo figures[28] report an incidence of 0.57% in the 14,900 cases.

The opinion often quoted, that the jejunum is least frequently the site of carcinoma, appears to have been based on analysis of the earlier reported series. Of 163 reported cases, including the Pondville series (Table 3), carcinoma is found in the duodenum 37%, jejunum 35%, and ileum 28%, showing that the duodenum and jejunum are more likely to undergo carcinomatous changes than the ileum. Sarcoma, on the other hand, most frequently occurs in the ileum.[6,32]

TABLE 3.—INCIDENCE OF CARCINOMA OF SMALL INTESTINE ACCORDING TO LOCALITY

Source	Duodenum	Jejunum	Ileum
Madyl[26]	2	0	4
Nothnagel[38]	5	0	6
F. Muller[34]	6	0	2
Meyer and Rosenberg[33]	4	3	3
Joyce,[23] 1932	1	2	1
Raiford[44]	5	4	3
Nickerson and Williams[37]	6	2	0
Medinger,[32] 1927–1939	3	11	2
Mayo Clinic[28]	23	31	21
Stein[52]	2	2	2
Jetter[22]	0	1	0
Pondville series	3	1	2
Total	60 (37%)	57 (35%)	46 (28%)

The distribution of carcinoma within the duodenum is not so easily analyzed. Dividing the duodenum into 3 parts (1st or preampullary, 2d or periampullary, and 3d or prejejunal), the periampullary region appears to be the most frequent site of carcinoma (Table 4), although there is some question whether, if carcinomas of proven origin in the duodenum alone were used, there would be much difference between the 1st and 2d portions. The 3d portion, however, is undoubtedly less frequently subject to malignant change although scattered cases are reported.[3,9,12,23,27,33,47,50,54]

TABLE 4.—INCIDENCE OF DUODENAL CARCINOMA ACCORDING TO PORTION OF ORIGIN IN DUODENUM

Source	1st portion	2d portion	3d portion
Meyer and Rosenberg[33]	0	3	1
Raiford[44]	2	1	2
Nickerson and Williams[37]	3	3	0
Dewis,[9] 1928	5	5	2
Mayo Clinic,[12] 1925	6	6	3
Mateer and Hartman,[27] 1932	1	4	1
Pic,[41] 1895	2	1	1
Pondville series	1	0	2
Total	20 (31%)	26 (45%)	12 (21%)

Etiology. The causation of carcinoma of the duodenum has been discussed for years without much clarification. Early writers inclined to associate cancer with preëxisting duodenal ulcers. Jefferson[21] col-

lected 30 such cases and after careful evaluation concluded, "that a causal relationship between simple ulcer and carcinoma is difficult to establish in the case of the duodenum." He reported that 99.2% of duodenal ulcers occurred in the 1st portion, which in itself is an argument against such an association. Dewis[9] felt that duodenal carcinoma probably developed independently and that there was little evidence for preëxisting ulcers. Many observers have been misled by the ulcerating nature of the carcinoma itself and it is quite probable that many of the so-called cases are in reality ulcers secondary to the cancer.

Malignant changes in aberrant gastric glands, pancreatic rests, and Brunner's glands have had many old and recent advocates. Bland-Sutton[2] commenting on these theories, thought that "they belong to the domain of fiction." Robertson[46] has recently reviewed a large number of duodenums and has only twice observed evidence of proliferative activity in Brunner's glands. After reviewing many of the recorded cases of Brunner's gland carcinoma, he concluded that hyperplastic and neoplastic involvements are very rare and that only a few of the reported cases of carcinoma arising from these glands could be accepted without reservations.

The relation of polyps and adenomas to duodenal carcinoma is still controversial. Raiford[44] found adenomas the most common benign tumor in the small intestines, with the highest incidence in the ileum, and thought that they were more susceptible to invasion by carcinoma because of their abnormal arrangement of epithelial lining. Saint[49] reported that 25% of all polypi occurred in the small intestines. In this group, there was only 1 adenoma and that was located in the duodenum. In the large intestines, 36 of 44 polypi were adenomas. Generally, however, most cases of malignancy of the small intestines are not associated with polyposis.[32] Geiser[16] maintained that the duodenal contents chronically irritated a fold of mucosa, producing cancer. Forgue and Chauvin[15] believed that the fixation of the parietal epithelium, the 4 flexures, and the fact that the duodenum was the most widely dilated portion of the intestines were in favor of duodenal carcinoma.

Heggs[20] associated the behavior of pyloric carcinoma, which freely infiltrates the stomach wall but declines to affect the duodenum, with the rarity of duodenal carcinoma. Nagel,[36] however, has shown that this limitation is more apparent than real and cites 48 of 256 compiled cases in which malignancy had macroscopically or microscopically extended beyond the pylorus. Rankin and Mayo[45] have always maintained that the fluid nature, the alkalinity, and the absence of abrupt bends explained the rarity of tumors of the small bowel. Raiford[44] has suggested that, due to the fact that the small intestine developed in the last 4 months of fetal life, it would be plausible to assume that there would be far less opportunity for arrested development and misplaced embryonic tissue than in the remainder of the gastro-intestinal tract.

Pathologic Anatomy. Carcinomas of the duodenum usually occur singly in either a stenosing or polypoid form. Eusterman, Berkman and Swan[12] found 13 stenosing types in their series of 15. Nickerson and Williams[37] found that the stenosing type predominated 3 to 1. The stenosing forms infiltrate into the tissues beneath the mucosa and tend to encircle the lumen. Ulceration and scirrhous replacement are common, causing obstruction by narrowing the lumen. The tumor occurs as an adenocarcinoma or an undifferentiated, medullary carcinoma. Fenwick and Fenwick[14] state that this type is more common in the 3d portion. Extensive carcinoma may occur in the 3d portion, however, without causing obstruction (Case 3). The polypoid type tends to be limited to the mucosa and occurs as a malignant adenoma or a papillary adenocarcinoma. The tumor is composed of large columnar or cylindrical cells with abundant cytoplasm and large, vesicular, hyperchromatic nuclei. Glandular differentiation varies from well-defined glands in the malignant adenomas to a few ill-defined acini in certain types of adenocarcinoma. Mucin may appear either in irregular spaces or in isolated groups of "signet ring cells." Obstruction may occur from blockage of the lumen. Judd[24] felt that this type of growth was more commonly found in the 1st portion.

In 1895, Pic[41] pointed out the difference between carcinoma of the papilla and duodenal carcinoma and noted that the former "as a rule, constitute circumscribed tumors that occupy only a portion of the intestinal wall and consequently resemble, in this respect, carcinomas that are situated in the head of the pancreas itself, whereas, true duodenal carcinoma show the same tendency that is so common in other forms of intestinal carcinoma, namely, to develop in an annular or cylindric manner and so involve the whole circumference of the intestine.

Metastases. Opinions vary on the time and extent of metastases. Generally, the bulk of evidence indicates that they are late and chiefly involve the regional lymph nodes followed more rarely by involvement of the mesentery, liver, lungs, peritoneum, supraclavicular nodes, and bone. Early writers mention metastases to the pancreas; but recent cases fail to substantiate these findings. Nickerson and Williams[37] observed this fact and concluded that "lack of pancreatic metastases emphasizes the necessity of carefully excluding primary carcinoma of the pancreas and that this factor may well explain the variation of incidence noted in other reported series." Craig[7] studied the lymph glands in carcinoma of the small intestines and found 36% eventually metastasized and observed that neither the size of the growth, the duration of symptoms, the size of the nodes, nor the number of palpable nodes was a reliable index of lymphatic involvement.

Signs and Symptoms. Carcinoma of the duodenum occurs approximately 3 times more often in males than females. The average age falls in the 6th decade with reported cases ranging from 17 to 84 years.

In 1899, Aaron[1] wrote, "For therapeutic reasons, the diagnosis of carcinoma of the duodenum should be made as early as possible, a task that requires the keenest medical acumen. In the majority of cases, the tumors are quite large when discovered, for when they are small

we do not get many symptoms so long as the lumen of the intestine is patulous." The truth of this statement still holds today and the problem of diagnosis is still a difficult one. Mayo[28] found, after reviewing 28 cases of carcinoma of the duodenum, that the diagnosis had been actually or tentatively made in 29.2%.

A majority of cases are characterized by a prodromal period of none too characteristic signs or symptoms. The complaints are chiefly referable to the stomach although they are often mistaken for chronic cholecystitis, peptic ulcer, or primary anemia.[3] Vague epigastric distress with occasional attacks of pain, anorexia, weakness, and loss of weight are usually present. Nausea and vomiting may occur, associated with recurrent attacks of intestinal obstruction. There is usually a moderate to marked anemia which frequently will be the only presenting symptom.[18] The anemia may be either macrocytic and hyperchromatic probably due to a failure of absorption of the Hematopoietic Principle of Castle, or microcytic and hypochromic due to blood loss and failure of absorption of iron. Plunkett, Foley and Snell[42] believed that the problem was one of absorption rather than of blood loss. Sowles,[51] on the other hand, thought that there would be no anemia unless ulceration occurred. Both types do occur, although the hypochromic type appears to be more common. In obstructive cases, there is marked alteration in absorption and severe blood loss occurs in the ulcerative type (Case 3). In a number of cases where the lesion has remained small and intact without causing obstruction the blood picture has remained essentially normal.

Occult blood in the stools is a rather consistent finding. The gastric analysis varies with a trend towards low or absent free hydrochloric acid. Cases are reported with hyperacidity.[19] Palpable tumor masses occasionally are reported but generally this sign is uncommon. Jaundice is rare even with involvement of the 2d portion, except in the terminal period. Early writers stressed this sign as characteristic of carcinoma of the 2d portion, and Mateer and Hartman[27] have recently reported its presence in 5 of 6 patients. The Mayo series[12] contrarily notes its absence. With infra-ampullary carcinoma, jaundice is characteristically absent.

As the malignant lesion progresses, many cause obstruction. At this stage, dehydration and toxemia occur as serious complications. McVicar,[31] and Eusterman, Berkman and Swan[12] report cases presenting shock, uremia, and tetany-like manifestations associated with a rise in blood urea, a fall in plasma chlorides, and a rise in the CO_2 combining power of the plasma.

Perforation of duodenal carcinomas is rare, but may abruptly cause the first symptom. Dewis[9] refers to an example of this in the first recorded case of Hambergers in 1746. Ylvisaker[56] recently reported a case of carcinoma of the 3d portion with perforation and formation of a localized abscess.

Occasionally death may occur from erosion of a blood-vessel. Mateer and Hartman[27] reported a case eroding the gastro-duodenal artery and Meyer and Rosenberg[33] an additional case. Case 3 of this

series died following rupture of the first jejunal branch of the superior mesenteric artery.

In the 1st portion of the duodenum, the symptoms simulate those of pyloric carcinoma. In the 2d portion, carcinoma of the duodenum may simulate carcinoma of the ampulla of Vater with jaundice, fever and sepsis. Outerbridge[39] felt that it was unnecessary to separate these groups, although pathologically they were different. In the 3d portion, carcinoma is characterized by bile in the gastric contents providing obstruction has occurred.

Roentgenograms are of increasing aid in the diagnosis of carcinoma of the duodenum, although much less reliable than in other portions of the gastro-intestinal tract. In over one-half of the proved cases, the Roentgen ray evidence has been negative. In Case 3 of this series, the gastro-intestinal series was negative on 4 different occasions with different examiners. Doub and Jones[10] and Raiford[43] list the following findings depending upon the stage of the disease and the amount of deformity and obstruction: (1) Dilatation and vigorous reverse peristalsis in which the tumor has caused obstruction; (2) filling defect more commonly an irregular narrowing but frequently simulating the picture of an ulcer. Harris and Green[17] advise the use of 1 to 3 hour films during a barium examination in order to obtain a full view of the duodenum. Mayo[28] recently reported additional aid in Roentgen ray diagnosis through the use of the Miller-Abbott tube.

Differential Diagnosis. The following conditions must be kept in mind. Malignant and benign pyloric obstruction, carcinoma of the head of the pancreas or gall bladder with involvement of the duodenum, carcinoma of the papilla or terminal portion of the common duct, inflammatory masses, peritoneal tuberculosis, angiomesenteric ileus, and actinomycosis, a rare condition reported by Wheeler.[55]

Prognosis. The average duration of reported case has been from 6 to 14 months. Unless diagnosed and treated early, the mortality is extremely high. Mayo[28] reports 8 cases (12.3%) surviving 5 years. Meyer and Rosenberg[33] refer to 2 cases operated with recovery, and Lundberg[25] and Syme[53] each have reported a case of carcinoma of the 3d portion with operation and recovery.

Case Reports.* CASE 1 (Pondville No. 111). A 65 year old male admitted on 10/12/27 with the complaints of epigastric pain and distress of 2 years duration, anorexia, weakness, and 30 pounds weight loss. His pain came on shortly before meals and was relieved by milk and soda. Six months before admission, he had begun noting tarry stools and there had been 1 severe intestinal hemorrhage. Physical examination revealed marked tenderness and spasm over the right rectus muscle above the umbilicus and a severe anemia. Upper gastro-intestinal Roentgen rays revealed the duodenum displaced to the right with a large filling defect in the 1st portion suggesting a chronic indurated ulcer. On 11/2/27, the patient died suddenly from hemorrhage.

Autopsy (partial) revealed a crater-like deformity just below the pylorus. Microscopic section revealed adenocarcinoma.

Diagnosis: Adenocarcinoma of 1st portion of duodenum.

* Cases 1 and 2 were recently included in a report by Ritvo and Hewes. Radiology. 38, 7, 1942

CASE 2 (Pondville No. 16472). An 80 year old male admitted on 11/15/39 complaining of epigastric distress, pains across the lower abdomen, weakness, and 27 pounds weight loss. For 2 months there had been constipation and tarry stools followed by diarrhea 3 weeks before admission. Previous to admission, he had been digitalized for heart disease. Physical examination revealed a marked anemia and a moderately enlarged liver. On 11/18/39, he suffered marked respiratory distress and expired within a few minutes.

Autopsy revealed the distal third of the duodenum almost entirely replaced by a stenosing tumor. The base and margin were indurated and along the floor there was evident thrombosed arteries. There were no metastases. In the lungs, the major branch of the left pulmonary artery, together with smaller right pulmonary arteries, were completely occluded by striated antemortem

FIG. 1a.—Case 2. (× 160.)

clots. Microscopic sections of the duodenal lesion revealed ramifying gland-like structures composed of crowded, acidophilic, cuboidal to cylindrical cells with large hyperchromatic nuclei showing a moderate number of mitoses. In some areas, the tumor cells appear piled up in less differentiated masses. Necrosis was marked (Fig. 1a and b).

Diagnosis: Adenocarcinoma of 3d portion of duodenum.

CASE 3 (Pondville No. 17235). A 48 year old male admitted 6/1/40. In May 1940, he had been seen outside with the complaints of abdominal pain, nausea, and vomiting of 2 years duration. Two gastro-intestinal Roentgen rays were reported negative. On entering Pondville, he was complaining of mild epigastric pain which came on at night and bore no relation to meals and was not relieved by food. His appetite was good and there was only a suggestive loss of weight. Physical examination revealed marked LUQ muscle

guarding with an associated pain running around the rib margin, a marked anemia (4.7 gm.—30%), stools positive for occult blood, hypoacidity of the gastric contents, and 2 negative gastro-intestinal Roentgen rays. On 6/29/40, the patient had a sudden fainting spell and the following morning he vomited large amounts of blood and a long, firm, blood cast. On 7/2/40, a rigid abdomen was noted and an immediate exploration was performed under local anesthesia by Dr. Donald Hight. The stomach and the 1st and 2d portions of the duodenum were found extending unusually far to the right. Exposure of the 3d portion released a large amount of fecal smelling fluid. The jejunum from the ligament of Treitz for a distance of 12 to 15 inches was gangrenous. The duodenal-jejunal angle was indurated and poorly defined. A Witzel enterostomy was performed in *lieu* of further surgery. The patient failed progressively and died on 7/4/40.

Fig. 1b.—Case 2. (× 35.)

Autopsy revealed the 3d portion of the duodenum together with the root of the mesentery, the medial portion of the pancreas, and the transverse colon matted together in a firm, suppurative mass. The duodenal-jejunal flexure was completely destroyed by a necrotic, gray-red, 10 cm. tumor mass which was continuous and indistinguishable from the involved medial portion of the pancreas. The edges of the ulcerating mass were indurated and rolled. The first jejunal branch of the superior mesenteric artery as it crossed the ulcerating mass was completely eroded and thrombosed. The regional nodes were enlarged and firm. Microscopically, sections of the tumor revealed irregular masses of tumor cells and gland-like structures composed of piled up, cuboidal cells with oval, vesicular, hyperchromatic nuclei containing prominent nucleoli and showing a moderate number of mitoses. Necrosis and round cell infiltra-

Fig. 2.—Case 3. (× 35.)
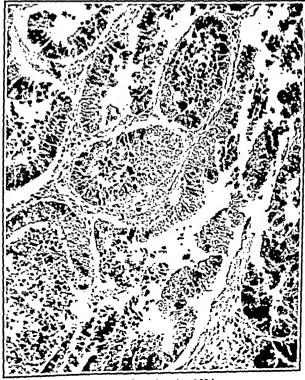
Fig. 3.—Case 3. (× 160.)

tion appeared throughout.   All of the lymph nodes were negative for tumor (Figs. 2 and 3).

Diagnosis: Adenocarcinoma of 3d portion of duodenum.

Summary and Conclusions.   Three cases of carcinoma of the duodenum are reported including one associated with erosion of the superior mesenteric artery.

In a review of the literature, excluding carcinomas of the pancreas and papilla, 55 carcinomas of the duodenum with an incidence of 0.047% in 117,433 autopsies are recorded.   Analyzing 10,340 cases of carcinoma of the intestines an incidence of small intestinal carcinoma is found to be 1.47%.   Of 163 cases of carcinoma of the small intestine, involvement of the duodenum is found in 37%, jejunum 35%, and ileum 28% indicating, contrary to frequently quoted opinion, the duodenum and jejunum are more likely to undergo carcinomatous changes than the ileum.   In the duodenum carcinoma appears in the 1st portion 34%, 2d portion 45%, and 3d portion 21%.

Carcinomas of the duodenum are generally conceded not to arise from preëxisting ulcers and are seldom associated with polyposis. The location of the duodenum and the nature of its contents explain more satisfactorily the rarity of tumors in this area.   When present, these tumors more commonly occur in a stenosing form and less frequently assume a polypoid structure.   They metastasize late and usually then only involve adjacent tissues.

A brief summary of signs and symptoms is presented.

REFERENCES

1. AARON, C. D.:   Philadelphia Med. J., 3, 280, 1899.
2. BLAND-SUTTON, SIR J.:   Lancet, 2, 931, 1914.
3. BOWERS, J. M., and MULLEN, B. P.:   Northwest Med., 35, 380, 1936.
4. BRILL, N. E.:   AM. J. MED. SCI., 128, 824, 1904.
5. CHOMEL: Gaz. d. hôp., No. 10, p. 37, 1852 (quoted by Dewis).
6. COHN, E. D.:   Surg., Gynec. and Obst., 43, 757, 1926.
7. CRAIG, W. McK.:   Surg., Gynec. and Obst., 38, 479, 1924.
8. DEAVER, J. B., and RAVDIN, I. S.:   AM. J. MED. SCI., 159, 469, 1920.
9. DEWIS, J. W., and MORSE, G. W.:   New England J. Med., 198, 383, 1928.
10. DOUB, H. P., and JONES, H. C.:   Radiology, 26, 209, 1936.
11. EGER, S. A.:   Arch. Surg., 27, 1087, 1933.
12. EUSTERMAN, G. B., BERKMAN, D. M., and SWAN, T. S.:   Collected Papers of the Mayo Clinic and Mayo Foundation, Philadelphia, W. B. Saunders Company, 17, 75, 1925.
13. EWING, J.:   Neoplastic Diseases, 4th ed., Philadelphia, W. B. Saunders Company, p. 721, 1939.
14. FENWICK, S., and FENWICK, W.:   Carcinoma and Other Tumors of the Stomach, Philadelphia, P. Blakiston's Son & Co., p. 284, 1903.
15. FORGUE and CHAUVIN: Rev. d. chir., 50, 470, 1915 (quoted by Nickerson and Williams).
16. GEISER, J. F.:   Deutsch. Ztschr. f. chir., 75, 41, 1907 (quoted by Deaver and Ravdin).
17. HARRIS, J. H., and GREEN, J. E.:   Am. J. Roentgenol., 43, 383, 1940.
18. HATCHER, A. R., and VOLDENG, K. E.:   Am. J. Digest. Dis. and Nutr., 4, 507, 1937.
19. HEAD, S. D.:   AM. J. MED. SCI., 157, 182, 1919.
20. HEGGS, F. M.:   Brit. J. Surg., 26, 532, 1939.
21. JEFFERSON, G.:   Brit. J. Surg., 4, 209, 1916-1917.
22. JETTER, W. W.:   New York State J. Med., 39, 1614, 1939.
23. JOYCE, T. M.:   Ann. Surg., 100, 949, 1934.
24. JUDD, E. S.:   Jour.-Lancet, 39, 159, 1919.
25. LUNDBERG, S.:   Acta. chir. Scandinav., 56, 417, 1924.

26. MADYL: Ueber den Darmkrebs, Vienna, 1883 (quoted by Nothnagel).
27. MATEER, J. G., and HARTMAN, F. W.: J. Am. Med. Assn., 99, 1853, 1932.
28. MAYO, C. W.: West. J. Surg., 48, 403, 1940.
29. McGLINN: New York Med. J., 93, 579, 1911 (quoted by Outerbridge).
30. McGUIRE, E. R., and CORNISH, P. G.: Ann. Surg., 72, 600, 1920.
31. McVICAR, C. S.: AM. J. MED. SCI., 169, 224, 1925.
32. MEDINGER, F. G.: Surg., Gynec. and Obst., 69, 299, 1939.
33. MEYER, J., and ROSENBERG, D. H.: Arch. Int. Med., 47, 917, 1931.
34. MULLER, F.: Arch. f. klin. Chir., 99, 305, 1912 (quoted by Jefferson).
35. MULLER, M.: Beitr. z. k. d. metast. malig. tumoren, Berne, 1892 (quoted by Jefferson).
36. NAGEL, G. W.: Arch. Surg., 11, 529, 1925.
37. NICKERSON, D. A., and WILLIAMS, R. H.: Am. J. Path., 13, 53, 1937.
38. NOTHNAGEL, H.: Diseases of the Intestines and Peritoneum, Am. Ed., Philadelphia, W. B. Saunders Company, p. 447, 1907.
39. OUTERBRIDGE, G. W.: Ann. Surg., 57, 402, 1913.
40. PERRY, E. C., and SHAW, L. C.: Guy's Hosp. Rep., 50, 171, 1893.
41. PIC: Rev. de méd., 15, 56, 1895 (quoted by Nothnagel).
42. PLUNKETT, J. E., FOLEY, M. P., and SNELL, A. M.: Canad. Med. Assn. J., 34, 289, 1936.
43. RAIFORD, T. S.: Radiology, 16, 253, 1931.
44. RAIFORD, T. S.: Arch. Surg., 25, 122, 1932.
45. RANKIN, F. W., and MAYO, C.: Surg., Gynec. and Obst., 50, 939, 1930.
46. ROBERTSON, H. E.: Arch. Path., 31, 112, 1941.
47. ROLLESTON, H. D.: Lancet, 1, 1121, 1901.
48. RUPP: Arch. f. klin. Chir., 99, 305, 1912 (quoted by Jefferson).
49. SAINT, J. H.: Brit. J. Surg., 15, 99, 1927.
50. SCHOFIELD, J. E.: Brit. J. Surg., 18, 84, 1930.
51. SOWLES, H. K.: New England J. Med., 210, 942, 1934.
52. STEIN, J. J.: Am. J. Digest. Dis. and Nutr., 4, 517, 1937.
53. SYME, G. A.: Lancet, 1, 148, 1904.
54. VICKERS, D. M.: Ann. Surg., 79, 239, 1924.
55. WHEELER, W. I. DE C.: Brit. J. Surg., 25, 753, 1938.
56. YLVISAKER, R. S.: Minnesota Med., 12, 351, 1929.

THE PREVENTION OF RENAL PRECIPITATION OF SULFADIAZINE IN DOGS

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PRECIPITATION of the sulfonamides or their acetyl forms in the urinary tract has recently[11] been shown to be one of the most serious complications resulting from therapy with these drugs. As yet, no uniformly successful method for preventing this complication has been reported. Alkalies have been tried, but there is no agreement as to their effectiveness; e. g., Peterson and Finland[9] stated that "Whether renal complications occur more frequently in an acid urine than an alkaline urine has been a subject of more speculation than objective study." It is the purpose of this experimental study to show that precipitation of sulfadiazine and its acetyl form in the urinary tract is a result of their insolubility in acid urine; but in alkaline urine they can be maintained in solution and renal precipitation thereby prevented.

. There are numerous reports in the literature showing that sulfapyri-

dine, sulfathiazole, sulfadiazine, and their acetyl forms are relatively insoluble drugs as compared with sulfanilamide. Curtis and Sobin[2] showed that the solubility of acetyl sulfathiazole is increased in alkaline urine. Sunderman and Pepper[10] showed that the solubility of sulfathiazole and acetyl sulfathiazole is increased in both phosphate buffer and urine in the higher pH ranges. Feinstone[4] found that sulfadiazine was more soluble in urine than water. These investigators also found that urea, glucose, sodium chloride, and high specific gravity did not significantly increase the solubility of these drugs in water or urine. Recently, however, Fox and Rose[5] showed that the solubility of sulfathiazole and sulfadiazine can be increased manyfold by allowing salt formation to occur in alkaline buffer.
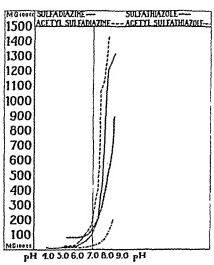
Fig. 1.—The variation in the solubility of sulfadiazine, sulfathiazole, and their acetyl forms in normal human urine from pH 5 to 8.5. *Horizontal axis:* Hydrogen-ion concentration (pH) of the urine at which drug levels were determined. *Vertical axis:* Mg. per 100 cc. concentration of drug in the urine showing the great increase in the solubility of these substances in alkaline urine.

The first step in the prevention of renal precipitation was to determine the solubility of the sulfonamides in urine over the physiologic pH range.[7] As seen in Figure 1, the solubility of these drugs in acid urine below pH 7 is relatively low, but above pH 7, in alkaline urine, the solubility is increased many times.

What is the explanation of this increase in solubility in alkaline urine? The answer lies in the chemistry of these compounds: They are weak acids which ionize and form salts which are relatively soluble.[6] It is this soluble salt formation which increases the solubility of sulfathiazole and sulfadiazine.* The importance of this fact may be realized by comparing the water solubility of these drugs with the urinary solubility (Table 1), and contrasting these findings with the incidence of renal complications.

* Experiments *in vitro* have shown that sulfanilamide has a higher antibacterial potency at pH 7.8 than at pH 6.8.[3]

TABLE 1.—COMPARISON OF WATER AND URINE SOLUBILITY

	Solubility in water at 25° C. (mg./100 cc.)	Solubility in urine at pH 7.4 (mg./100 cc.)	No. of times increase in solubility
Sulfapyridine	37	60	1.6
Sulfathiazole	60	220	3.6
Sulfadiazine	8	280	35.0
Sulfanilamide	1000	1700	1.7

Sulfanilamide is the most soluble in both water and urine, and the solubility of this drug and its acetyl form is well in excess of the urinary levels obtained during therapy; there are few, if any, instances of its renal precipitation.

Sulfapyridine represents the other extreme in that it is relatively insoluble in water, and its urinary solubility is only slightly increased by ionization; accordingly, in urine it is the least soluble of all the drugs, and alkaline therapy can improve this but slightly (Table 1). It is generally agreed that therapy with this drug produces the highest incidence of renal obstruction.

Sulfadiazine is the least soluble in water, but its solubility is increased over 30 times in urine at pH 7.4 as a result of ionization. At this pH, sulfadiazine has a higher urinary solubility than the other sulfonamides except sulfanilamide; but at pH 6.5, its solubility is the lowest.

Sulfathiazole has a higher water solubility than sulfadiazine, but the increase in its solubility by ionization is much less (3.6 times); consequently, its solubility in urine at pH 7.4 is also less.

The acetyl derivatives likewise can ionize to form soluble salts. Acetyl sulfapyridine, however, ionizes only slightly, and accordingly, its very low water solubility is but scarcely increased within the physiologic pH range (30 mg. at pH 8). Acetyl sulfathiazole is even less soluble in water (7 mg.), but this is increased considerably by ionization, as seen in Figure 1 (60 mg. at pH 8). Acetyl sulfadiazine differs from the others in that it is slightly more soluble than the free form (15 cf 12 mg. at 37° C.), and it is more extensively ionized than any of the drugs including the free form so that at pH 7.5 a concentration of 1000 mg. may be obtained.

The solubility of the sulfonamides may be summarized as follows: Sulfanilamide and its acetyl form, although only slightly ionized within the physiologic pH range, are relatively soluble in both water and urine. Sulfapyridine and its acetyl form, relatively insoluble in water, are very slightly ionized, and remain very poorly soluble in urine. Sulfathiazole, sulfadiazine, and their acetyl forms are also relatively insoluble in water, but their high degree of ionization and salt formation increases many times their solubility in urine above pH 7.

From a practical point, it seems important to determine whether precipitation of sulfadiazine might occur when the urine is acid, and might be prevented when the urine is alkaline. Experiments were then conducted on dogs to determine whether it is possible by the administration of sodium bicarbonate to raise the urinary pH and thereby increase the ionization (and solubility) of sulfadiazine suffi-

ciently to prevent its precipitation in the urinary tract. This was compared with the results obtained in acid urine when ammonium chloride was administered. These experiments were conducted in three parts, as follows:

Experiment A. Ammonium chloride and sodium bicarbonate were administered orally with sulfadiazine to determine the effect of acids and alkalies on drug excretion and crystalluria.

Experiment B. Sodium bicarbonate was administered with powdered and enteric coated sodium sulfadiazine to compare the effect of alkalies on gastro-intestinal absorption and urinary excretion.

Experiment C. Sulfadiazine was given subcutaneously to eliminate variations due to gastro-intestinal absorption: Sodium bicarbonate and ammonium chloride were administered by mouth.

EXPERIMENT A. The renal excretion of sulfadiazine in relation to urinary pH.

Method. Sulfadiazine* (0.2 gm. per kilo of body weight) was administered by mouth daily for 44 days to two normal dogs. During the first 14 days sulfadiazine alone was given (control period). For the next 6 days equal amounts of sulfadiazine and sodium bicarbonate were given (alkali period). For the next 7 days they received 0.5 gm. enteric coated ammonium chloride in addition to the sulfadiazine (acid period). Finally, they were given equal doses of sulfadiazine and sodium bicarbonate for the last 11 days. All drugs were administered in fresh chopped meat. The fluid intake (unrestricted) was recorded for each 24 hour period. The dogs remained in metabolism cages throughout the entire experiment. Blood sulfadiazine levels were done twice weekly. Urine specimens were collected as voided during the day, and toluol was added to the collecting flasks for the overnight specimens. The quantity, specific gravity, pH and sulfadiazine level of each urine specimen was determined.† The pH was measured with the Beckman glass electrode pH meter. The sulfadiazine levels were determined by a modification of the Bratton-Marshall method[1] using a Klett-Summerson photoelectric colorimeter with a No. 54 filter. The sulfadiazine levels were done ·in duplicate and checked within 2%. The majority of determinations checked within 1%.

From this data the daily excretion was determined, and the average percentage of sulfadiazine excreted in 24 hours was computed.

Results. (a) The pH of the urine was raised during the sodium bicarbonate period and lowered during the ammonium chloride period. The "average" urinary pH during the three periods was as follows:

	Male (pH)	Female (pH)
Control	6 52	7 04
Sodium bicarbonate	7 19	7 25
Ammonium chloride	6 05	6 16

(b) The urinary sulfadiazine levels fluctuated with the changes in urinary pH induced by the two adjuvant drugs employed (Fig. 4).

(c) Twenty-four hour urinary excretion of sulfadiazine varied directly with the pH (Fig. 3, Table 2).

(d) During the ammonium chloride period, crystals of sulfadiazine were present in the urine of both dogs. At this stage of the experi-

* The sulfadiazine used in these experiments was supplied by Lederle Laboratories and E. R. Squibb & Sons.
† Since dogs do not acetylate the sulfonamides,[2] this determination was unnecessary.

ment a quantitative method for measuring the amount of solid drug not in solution was devised[7] and conducted as follows: 50 cc. of each specimen of urine was centrifuged, and a sulfadiazine determination was done on 1 cc. of the supernatant and on 1 cc. of the sediment.   In a number of instances a significant difference between the two determinations was encountered, indicating the presence of large amounts of solid drug in the urine which was not in solution and which was thrown down by centrifugation.

TABLE 2.—THE EFFECT OF SODIUM BICARBONATE AND AMMONIUM CHLORIDE ON THE DAILY RENAL EXCRETION OF SULFADIAZINE BY DOGS RECEIVING CONSTANT DOSAGE OF DRUG

	Average daily excretion of sulfadiazine				Average increase + or decrease − from control period			
	Grams		Per cent		Grams		Per cent	
	M	F	M	F	M	F	M	F
Control	1.29	1.15	40.3	60.5				
Sodium bicarbonate .	2.04	1.39	63.9	73 1	+.75	+.24	+58	+21
Ammonium chloride .	0.85	0.73	26 5	38 4	− 45	− 42	−35	−36

Dosage: 0.2 gm. sodium bicarbonate per kilogram body weight; male, 3.20 gm.; female, 1.99 gm.

(e) Both dogs were then given sodium bicarbonate again, and with the rise in urinary pH, the undissolved sulfadiazine in the urine disappeared, and the supernatant and sediment levels approximated one another.   The urinary sulfadiazine levels again exceeded those obtained during the control and ammonium chloride periods.

(f) Blood sulfadiazine levels averaged 30.8 mg. for the male, and 15.6 mg. for the female.   The blood levels did not vary significantly from one period to the next.

Comment.   The increase in solubility of sulfadiazine above pH 7 is a result of increased ionization with formation of soluble salts.   If the pH of the urine remains above 7, the solubility is increased and the likelihood of renal precipitation is diminished.

Figure 2 shows the pH and mg. level of each individual specimen of urine throughout the entire experiment.   It will be noted that in acid urines (below pH 7), the urinary drug levels are considerably lower than those in alkaline urines (above pH 7).   Furthermore, many of the levels above 200 mg. in specimens below pH 7 are false levels; i. e., during the ammonium chloride period there was solid drug in the urine, and these concentrations do not represent sulfadiazine in solution (encircled points, Fig. 2).   This is most marked in the male.   The pH of the female urine was consistently higher than the pH of the male urine.   Likewise, the per cent of drug excreted per day by the female was higher, and the amount of solid drug in the female urine was consistently less.

There is a close correlation between the effect in vitro of pH on drug solubility and the results of these experiments.   When an average line is drawn through the concentration points (Fig. 2), the resulting curve is similar to the in vitro solubility curve (Fig. 1).   In both dogs the solid drug disappeared when the pH of the urine exceeded 7.   There are several exceptions to this.   In Figure 2 the dots with the circles

represent specimens in which there was considerable solid drug. In the male there are 4 specimens above pH 7 which contained solid drug. If reference is made to Figure 1, it will be seen that the concentration of drug in 3 of these exceeds the solubility limits of sulfadiazine. This is further confirmation of the relation between pH, urinary levels, and renal precipitation.

The purpose of Experiment B is to determine whether the oral administration of sodium sulfadiazine will maintain a higher urinary pH than is obtained with sulfadiazine, and thereby avoid renal precipitation.
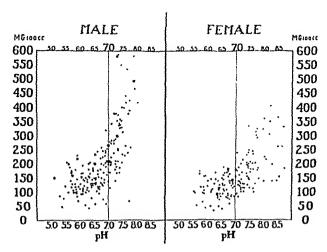
Fig. 2.—The occurrence of crystalluria in relation to the pH and drug concentration of the voided urine. *Horizontal axis:* The pH of the freshly voided urine. *Vertical axis:* Sulfadiazine level in mg. of each specimen. Encircled points represent specimens containing solid drug.
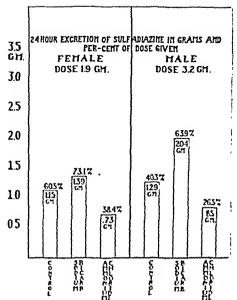
Fig. 3.—The effect of sodium bicarbonate and ammonium chloride on the daily renal excretion of sulfadiazine by dogs receiving constant dosage of drug.

Experiment B. *Method.* Sodium sulfadiazine was given orally in equimolar doses corresponding to the dose of sulfadiazine given in Experiment A.

The same two dogs were used in this experiment. Following a control period (sodium sulfadiazine only) lasting 9 days, they were given sodium bicarbonate for 10 days, but in smaller doses so that the total quantity of sodium given was equal to that in Experiment A.

This experiment was then repeated using enteric coated sodium sulfadiazine to avoid precipitation of free sulfadiazine by the hydrochloric acid in the stomach. The same routine of blood and urine analyses were employed as in Experiment A.

Results. (a) The pH values of the individual urine rspecimens were approximately the same with enteric coated sodium sulfadiazine as with the powdered sodium sulfadiazine and were no higher than during the administration of free sulfadiazine alone. When sodium bicarbonate was administered so that the total quantity of sodium (including sodium sulfadiazine) equaled the amount of sodium given as bicarbonate with the free sulfadiazine, there was the same rise in urinary pH as described in Experiment A.

(b) The urinary sulfadiazine levels during the sodium bicarbonate period again exceeded those obtained during the control period.

(c) Crystals of drug were found in only one urine specimen throughout this experiment, and in this instance only was there a significant variation between the supernatant and sediment determinations.

(d) Twenty-four hour urinary excretion of sodium sulfadiazine, either powder or enteric coated, was similar to the results obtained with the free drug. The increased drug excretion with the additional sodium ion was also similar.

	Male		Female	
	average daily excretion Dose 3.21 gm. (sulfadiazine)		average daily excretion Dose 1.83 gm. (sulfadiazine)	
	Grams	Per cent	Grams	Per cent
Control	1.35 (1.35)*	42.4 (42 3)	0 82 (1.06)	44.3 (55 5)
Sodium bicarbonate .	1.88 (1.82)	58.5 (57.0)	1.20 (1.15)	64.9 (60.2)

* Figures in parentheses are values obtained with powdered sodium sulfadiazine.

(e) Blood sulfadiazine levels averaged 24.8 mg. for the male, and 15.7 mg. for the female. Again, there were no significant variations from one period to the next.

Comment. Sodium sulfadiazine is presumably converted to sulfadiazine in the acid contents of the stomach. The purpose, therefore, of giving the enteric coated sodium sulfadiazine was to eliminate this conversion in the stomach. It has, however, been shown that the small intestinal contents are also acid,[3] so that prior to absorption, most of the salt is changed to the acid form, regardless of the enteric coating. At the time of absorption, or just afterwards, the drug is in the alkaline environment of the blood (pH 7.4) and almost completely ionized.[5]

Since the alkali or acid therapy might have influenced gastro-intestinal absorption of sulfadiazine and secondarily altered the rate of excretion, it was decided to administer the drug subcutaneously to eliminate this factor in the following experiment.

When sodium sulfadiazine (0.2 gm. per kilo) was given subcutaneously, the urinary levels were far in excess of the levels obtained by

oral administration, and the blood levels were also higher (better absorption). As there was considerable solid drug not in solution in the urine, it was necessary to reduce the dose by half to 0.1 gm. per kilo.

EXPERIMENT C. *Method.* Two normal dogs were given 0.109 gm. sodium sulfadiazine (equivalent to 0.1 gm. sulfadiazine) per kilo of body weight, by injecting a 5.6% solution into the region of the shoulders.* The male dog received 32 cc.; the female, 18.5 cc. each day for 30 days. This experiment was again divided into three periods: a control, a sodium bicarbonate, and an ammonium chloride period, each lasting 10 days. The sodium bicarbonate and ammonium chloride were administered by mouth, as in the previous experiments.

In addition to the routine blood and urine analyses employed in Experiment A, specimens of blood were collected under oil at various intervals throughout the three periods for pH measurement.
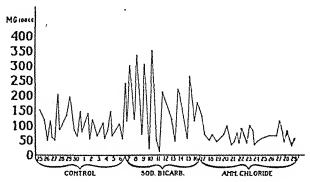
FIG. 4.—The variations in the urinary concentration of sulfadiazine with adjuvant therapy. (The same dose of sulfadiazine was administered throughout the three periods. Crystals of sulfadiazine were abundant during the ammonium chloride period and were rare during the sodium bicarbonate period. The same results were obtained when the drug was given orally or subcutaneously.)

Results. The urinary sulfadiazine levels were again elevated during the sodium bicarbonate period, and depressed during the ammonium chloride period (Fig. 4).

(b) The "average" urinary pH is shown in the following table:

	Male (pH)	Female (pH)
Control	6 28	7 19
Sodium bicarbonate	7.12	7 83
Ammonium chloride	6 17	6 95

(c) Twenty-four hour urinary excretion of subcutaneously administered sodium sulfadiazine:

	Male Dose 1.66 gm. (sulfadiazine) average daily excretion		Female Dose .96 gm. (sulfadiazine) average daily excretion	
	Grams	Per cent	Grams	Per cent
Control	1.09	65 5	.82	85 2
Sodium bicarbonate	1 28	77 1	.79	82 1
Ammonium chloride	0 89	53.6	.55	57 3

* There was no evidence of infection or irritation in the subcutaneous tissues during the 30-day period. There was only slight induration of the tissue at the sites of injection.

(d) The variation in the pH of the blood specimens during the three periods did not exceed 0.06.   The highest pH was 7.25, the lowest 7.19.

(e) Blood sulfonamide levels averaged 15.8 mg. for the male, and 11.7 mg. for the female.   There were no significant variations in blood levels during the three periods.

Comment. During the three periods there was no significant change in blood pH, and presumably the rate of absorption of sulfadiazine from the subcutaneous tissues remained constant. There was, however, the same increase in sulfadiazine concentration in the urine during the sodium bicarbonate period, and decrease during the ammonium chloride period (Fig. 4) as seen in the experiments with oral administration of the drug.

The drug output of the male dog, as in previous experiments, increased during alkali therapy, and decreased during acid therapy. This was also true for the female, except that the control pH was high (7.19), and at this pH the solubility of sulfadiazine is above the concentration obtained in the urine specimens in this experiment. Accordingly, during the alkali period, although both pH and drug level increased, the 24 hour excretion did not, partly because of diminished fluid intake.

Discussion. Alkali therapy was originally used with sulfanilamide to combat acidoses; but subsequently this was discontinued. When sulfapyridine was introduced, renal obstruction was frequently encountered, and alkalies were again administered in an effort to prevent this complication. Alkalies do not prevent precipitation of sulfapyridine, since they increase its solubility but slightly.[2] The solubility of sulfathiazole and sulfadiazine, on the other hand, is greatly increased by alkali therapy provided the urinary pH is maintained above pH 7. To accomplish this, sufficient alkali is required to neutralize the acidity of sulfadiazine itself in addition to the urinary acidity.

Why does one patient receiving sulfadiazine have renal precipitation of the drug, and another patient receiving the same dosage have no evidence of renal obstruction? Since there is a wide (individual) variation in the pH of urine, it seems logical that the person with a consistently acid urine would be the most likely to precipitate the drug in the kidneys.

These relationships are particularly essential when large doses of drugs are given. For example, if a patient absorbs 6 gm. of sulfadiazine per day and has an average daily output of 1500 cc. of urine, it would require an average urinary level of 400 mg. to excrete the total quantity in 24 hours. Doubling the daily output of urine might halve the urinary sulfonamide concentration, but this level would still be far in excess of the solubility of the drug, and a pH above 7 (preferably 7.5) would be needed to insure solution.

The administration of acids or alkalies during sulfadiazine therapy changed the quantity of drug excreted regardless of the mode of administration. When the drug was given by the subcutaneous route, there was the same increase in excretion during alkali therapy and decrease in excretion during acid therapy as occurred when sulfadiazine was given

orally.   This would indicate that acid and alkali therapy do not alter the extent of absorption of sulfadiazine from the gastro-intestinal tract but alter the rate of excretion (and reabsorption) by the kidney.

There was no correlation between specific gravity and drug excretion. Low specific gravities were obtained with high urinary concentration levels and *vice versa*.   The specific gravity of specimens containing solid drug not in solution were evenly distributed from 1008 to 1030.

'Summary.   The effect of pH on the solubility of sulfadiazine has been demonstrated *in vitro* and *in vivo* in these experiments.   Insoluble sulfadiazine becomes relatively soluble as salt formation is induced by raising the urinary pH (Fig. 1).

Experiments in dogs showed that when the pH of the urine exceeds 7, crystalluria is minimal, higher urinary concentrations of drug are obtained, and the total quantity of drug excreted is likewise higher (Fig. 2).   Conversely, during acid therapy, when the urinary pH was below 7, crystalluria was marked, urinary levels were low, and the total quantity of drug excreted was considerably less.

A comparison of the pH and sulfadiazine levels in the urine specimens of dogs under therapy gave a curve (Fig. 2) that closely simulates the *in vitro* solubility curve (Fig. 1).

The subcutaneous administration of sulfadiazine (Experiment C) increased considerably the degree of absorption of sulfadiazine so that smaller doses had to be used.   Following the administration of sodium bicarbonate, there was the same increase in urinary pH and urinary sulfonamide concentration as occurred with the oral administration of sulfadiazine.   Acid therapy lowered the pH and reduced the urinary sulfadiazine concentration and total drug excretion.

It has been shown in these experiments that raising the urinary pH above 7 by the use of sodium bicarbonate is effective in increasing the solubility of sulfadiazine and preventing its precipitation in the kidneys of dogs.   This increased solubility of sulfadiazine in alkaline solutions further suggests a method of treatment of renal obstruction resulting from the precipitation of the sulfonamides.   In the ureteral and pelvic lavage therapy of sulfonamide renal obstruction, alkaline bicarbonate or carbonate solutions are recommended, since these will dissolve drug crystals much better than warm water or normal saline solution.   These methods of prophylaxis and treatment are under clinical trial.

REFERENCES

1. BRATTON, A. C., and MARSHALL, E. K., JR.:   J. Biol. Chem., 128, 537, 1939.
2. CURTIS, A. C., and SONIN, S. S.:   Ann. Int. Med., 15, 884, 1941.
3. EASTMAN, I. M., and MILLER, E. G.:   Proc. Soc. Exp. Biol. and Med., 30, 332, 1932.
4. FEINSTONE, W. H., WILLIAMS, R. D., WOLFF, R. T., HUNTINGTON, E., and CROSSLEY, M. L.:   Bull. Johns Hopkins Hosp., 47, 427, 1940.
5. FOX, C. L., JR., and ROSE, H. M.:   Proc. Soc. Exp. Biol. and Med., 50, 142, 1942.
6. FOX, C. L., JR.:   Arch. Surg., 45, 754, 1942.
7. JENSEN, O. J., JR., and FOX, C. L., JR.:   J. Urol., 49, 334, 1943.

8. Marshall, E. K., Jr., Cutting, W. C., and Emerson, K., Jr.: Science, 85, 202, 1937.

9. Peterson, O. L., and Finland, M.: Am. J. Med. Sci., 202, 757, 1941.

10. Sunderman, F. W., Pepper, D. S., and Benditt, E.: Am. J. Med. Sci., 200, 790, 1940.

11. Sutliff, W. D., Halpern, M., Griffin, G., and Brown, H.: J. Am. Med. Assn., 121, 307, 1943.

CLINICAL AND EPIDEMIOLOGICAL FEATURES OF AN OUTBREAK OF PRIMARY ATYPICAL PNEUMONIA OF UNKNOWN ETIOLOGY AMONG HOSPITAL AND MEDICAL SCHOOL PERSONNEL

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When an epidemic of primary atypical pneumonia abruptly involved the student body and staff of the University of Rochester School of Medicine and Dentistry and the Strong Memorial Hospital, it was realized that this outbreak among a closed group of known clinical and roentgenographic background afforded an unusual opportunity to investigate this malady. Accordingly, the earliest sign of illness was considered adequate reason for hospitalization. In each case repeated bedside observations and laboratory studies were made in an effort to learn more about these aspects of this disease. The purpose of this paper is (1) to report the clinical findings in 40 cases from the institutional personnel who were hospitalized with definite roentgenographic evidence of pneumonia between August 1 and September 30, 1942; and (2) to present the results of epidemiologic studies of a slightly larger group of patients and 1587 contacts. The epidemiologic investigations were carried out with the following objectives: (a) to compare the chronologic distribution of cases among institutional personnel with that among other persons in the community admitted to the same hospital; (b) to determine, if possible, the explanation for any significant differences in the incidence of the disease in various subdivisions of the institutional personnel; (c) to evaluate the contagiousness of the disease; (d) to determine whether the chief means of spread of the disease was through clinically recognizable cases or through subclinical cases and carriers.

Clinical Features. The age distribution of patients in this series was restricted; all but 3 were between 19 and 30 years of age; the oldest was 49. There were 32 males and 8 females, nearly all of whom were previously in good health. The relative homogeneity of this group of patients and the circumscribed nature of the outbreak make it apparent

that a single etiologic agent was responsible for virtually all of the cases. The clinical features for the most part resembled those described by others.[3,4,6,9-12,14,15]* There were no fatalities.

Symptoms. In most instances, the onset was insidious with prodromal symptoms of malaise, generalized aching and sore throat lasting 1 to 7 days. Because sore throat and aching appeared very commonly at an early stage of the disease, persons with these symptoms were regarded with great suspicion during the epidemic, whereas those with simple coryza were thought to be much less liable to develop atypical pneumonia. The acute phase of the illness in half the cases began with chilly sensations, but only 3 had frank, shaking chills. Every patient soon developed a persistent cough which was very disturbing and was relieved neither by cough mixtures nor by steam inhalations. Although the most severely ill patients suffered considerable dyspnea during the stage of maximum pulmonary involvement, and especially after severe paroxysms of coughing, this was noted later in the course of the illness and was less prominent than in comparable cases of pneumococcal pneumonia. This might also be said for cyanosis in these same patients, although cyanosis was more prominent than indicated in reports of other outbreaks of this same type of illness. Although pleural pain was suffered by only 1 patient, half of the patients complained of severe substernal pain which was thought to originate in the trachea because the onset coincided with that of the cough. The more frequently encountered symptoms are listed in Table 1.

TABLE 1.—INCIDENCE OF SYMPTOMS IN 40 PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA

Symptom	No. patients
Cough	40
Headache	33
Generalized aching	33
Sore throat	30
Backache	25
Chilliness	21
Tracheal pain	20
Eye pain	14
Dyspnea	12
Coryza	9
Mental confusion	4
Pleural pain	1

Signs. In many cases, a relative bradycardia was recorded but in the more severely ill patients tachycardia developed just before or during the period of lysis. The respiratory rate was significantly increased only in the cases with extensive pulmonary involvement and those complicated by asthma or wheezing. The temperature charts showed wide variations depending upon the severity of the case, but in general, the fever records can be placed in 3 groups: (1) Twenty patients with considerable pulmonary involvement and prostration had fluctuating fever for from 5 to 11 days with daily peaks of 39° to 41° C.

* Since the literature on primary atypical pneumonia has recently been reviewed by Dingle and Finland,[2] references given in this paper are limited to those which are specifically related to the contents of this report.

in the afternoon or evening; this was followed by lysis over a period ranging from 2 to 4 days. (2) Thirteen moderately ill patients had a similar type of fever for less than 5 days. (3) The 7 mild cases had only a slight remittent fever for 1 to 8 days. None of the patients included in this study had a sustained high plateau of fever and none developed herpes labialis simplex, but herpes has been noted in 2 of 4 more recent cases with relatively prolonged high fever. Once the temperature had fallen for a day or more, there was very seldom any secondary rise such as that reported by Longcope.[11]

Slight cervical lymph node enlargement was noted in several patients during convalescence. The only patient with a palpable spleen was a medical student known to have congenital hemolytic jaundice. Although Kneeland and Smetana[9] have reported arthritis, dermatitis, pericarditis and jaundice in severely ill patients, none of these extrapulmonary findings was noted in the group under consideration.

Chest findings on admission were usually minimal or absent even though there was definite evidence of pneumonia by Roentgen ray. Most frequently the earliest signs were slight dullness and fine, dry râles late in inhalation or only post-tussively. Just before or during the period of lysis and clinical improvement râles became more moist and abundant and far more widespread, but tubular breathing was seldom heard. In general, the chest signs and Roentgen ray findings were very similar to those described by others.[3,4,6,9–12,14,15] The distribution of pulmonary lesions according to lobes (Table 2) was much the same as is seen in pneumococcic pneumonia. This similarity has also been noted by Dingle et al.[4]

TABLE 2.—LOCATION OF PULMONARY LESION IN 40 PATIENTS WITH PRIMARY ATYPICAL PNEUMONIA AS DEMONSTRATED BY PHYSICAL SIGNS AND ROENTGENOGRAPHS

Lobe involved	No. cases
Right lower	11
Right middle	1
Right upper	2
Left lower	12
Left upper	2
Right lower and left lower	8
Other combinations	4
Total	40

Pleural effusion was suspected in 4 cases by physical signs and in 3 of these by Roentgen ray, but was proven in only one case by thoracentesis with removal of clear, yellow fluid which was bacteriologically sterile.

Roentgenographic Findings. The earliest change in the chest roentgenograph was a prominence of basal bronchovascular markings extending from the hilus as a fan-shaped shadow. Often this change was appreciated only by comparison with previous films which were available in nearly every case. Homogeneous shadows of low density were later superimposed upon these linear markings. Extension of the fan-shaped density toward the periphery was noted next, and in the more severe infections there was a mottled bronchopneumonic type of

infiltration. The resemblance to the Roentgen ray picture of pulmonary tuberculosis was sometimes striking. Actually at the time of maximal roentgenographic change, the patient had already begun to improve clinically.

In some cases the initial Roentgen ray finding was a basal shadow of considerable density which was not unlike that seen in pneumococcal pneumonia.

Asthma. Asthmatic wheezes were noted in 15 cases during the stage of resolution. One patient was convalescing from a mild attack of the disease when he was exposed to ragweed pollen and developed severe asthma, followed by a serious exacerbation of pneumonia. He was the only one who had suffered from asthma during previous ragweed seasons. Another patient had moderately severe asthma for several days. The remaining 13 patients had definite wheezing and prolongation of expiration with some degree of respiratory difficulty. Of the 40 persons under consideration, 10 gave a history of previous allergic disease (asthma, allergic rhinitis, hives or migraine). It is statistically significant that 8 of these 10 persons developed asthma or wheezing during the stage of resolution, whereas of the 30 patients with negative allergic histories, only 7 developed wheezing. Kneeland and Smetana[9] and Longcope[11] have also noted obstructive or asthmatic type of breathing but have not commented upon it from the standpoint of allergy. Its exact significance remains to be determined by further observations.

LABORATORY FINDINGS. *Sputum* was scanty and thin in the early stages of the disease but later it usually became grayish green, mucoid and more abundant. Blood streaking was noted only after paroxysms of coughing in severely ill patients. On the basis of the pathologic findings in the lungs of the few fatal cases of this disease, one might expect the sputum to be laden with mononuclear leukocytes, but actually the cellular content varied greatly. Some sputum smears showed a predominance of polymorphonuclear leukocytes; in others, mononuclear cells were more abundant and in still others, the two types of cells were equally divided. No correlation between the stage of the disease and the cellular content of the sputum could be established.

Bacteriologic Studies. Smears of sputum stained by the Ziehl-Neelsen technique were prepared at least once in each case but no acid-fast bacilli were found.

Cultures of sputum usually showed diphtheroids, *Neisseria catarrhalis*, *Streptococcus viridans*, *Hemophilus influenzæ*, *Staphylococcus aureus* and *Staphylococcus albus*. In a few instances pneumococci of the higher types were isolated by mouse inoculation but they were never present in great numbers on rabbit's blood agar plates inoculated with sputum. Repeated cultures of sputum failed to reveal any convincing evidence of secondary bacterial invasion in this disease, but 3 patients had many colonies of beta-hemolytic streptococci in their throat cultures late in the acute phase of their illness.

Blood cultures were obtained 1 to 4 times from every case and all were negative.

Isolation of a virus from sputum, nasal washings and stools by serial passage through mice and chick embryos was attempted without success.

Immunologic Studies. Blood serum was collected from many of the patients on admission and again at 1 month after the onset of illness. These specimens are to be tested for antibodies against a number of the viruses known to cause respiratory infection in man and in some animals. Thus far, 26 convalescent sera have been tested by complement fixation for *Rickettsia burneti* with negative results.*

Sheep-cell Agglutination. Fifteen admission specimens and 19 convalescent specimens were tested for sheep-cell agglutination. The technique consisted of mixing 0.5 ml. of serial dilutions of inactivated serum with 0.5 ml. of a 2% suspension of washed sheep cells, after which 1 ml. physiologic saline solution was added to each tube to bring the total volume up to 2 ml. After the tubes had incubated at 37° C. for 2 hours, they were placed in a refrigerator at 4° C. and read the following morning. The results as shown in Table 3 are inconclusive, especially when one considers the sheep-cell agglutination titers reported for normal human serum.[2] However, the fact that 1 patient, whose serum was negative on admission, developed during convalescence a titer of 1:64 and another a titer of 1:512 may be significant. In neither of these cases was the blood picture suggestive of infectious mononucleosis. Altogether 5 of 11 patients whose admission sera were negative developed sheep-cell agglutinins during convalescence.

TABLE 3.—RESULTS OF TESTS FOR SHEEP CELL AGGLUTININS IN PATIENTS' SERA TESTED ON ADMISSION AND DURING CONVALESCENCE

Titer* on admission	No. sera	Titer* of corresponding sera when tested 25 to 40 days after onset of illness					
		Negative	1:8	1:16	1:32	1:64	1:512
Not tested . .	4	0	1	2	1	0	0
Negative . .	11	6	0	2	1	1	1
1:8	3	2	1	0	0	0	0
1:16 . . .	1	0	0	1	0	0	0
Totals	19	8	2	5	2	1	1

* Titers are expressed in terms of final dilution of serum after addition of sheep cell suspension and saline.

Leukocyte Response. The white blood cell counts recorded on the day of admission to the hospital are shown in Table 4. During the early part of their illness, most of the patients had a white blood count within or near the normal range. During or soon after the period of lysis, 11 of the most severely ill patients developed a leukocytosis ranging from 12,000 to 20,000 cells per c.mm., and in more recent cases counts as high as 25,000 have been recorded at this stage of the disease.

* The complement-fixation tests with *Rickettsia burneti* were performed by Dr. Ida A. Bengtson, Senior Bacteriologist, and reported through Dr. Charles Armstrong, Chief of the Division of Infectious Diseases, National Institute of Health, Bethesda, Md.

In the majority of instances, a slight neutrophilia and shift to the left were noted whenever there was an appreciable leukocytosis. Monocytosis of 10 to 25% was recorded in 11 cases on admission and another patient had 25% monocytes in her blood smear during the early phase of convalescence. At various stages of the disease, an eosinophilia of 5 to 11% was noted in 8 cases. These differential white blood cell counts were made by a number of persons and only 100 cells were counted in each smear. The errors, both technical and unavoidable[1] in such counts are acknowledged.

TABLE 4.—TOTAL WHITE BLOOD CELL COUNTS IN 40 CASES OF PRIMARY ATYPICAL PNEUMONIA ON DAY OF ADMISSION TO THE HOSPITAL

White blood cells per c.mm.	No. patients in given range
3,000– 6,000	6
6,000– 9,000	18
9,000–12,000	11
12,000–15,000	5

Therapy. Treatment in all cases was largely symptomatic. Sulfadiazine was given to 16 patients at various stages of the disease but did not appear to alter the course of the illness.

Eight patients were given plasma (100 to 300 cc.) or whole blood (300 to 900 cc.) withdrawn from persons during the first 2 to 4 weeks of their convalescence from the same type of illness. Since September 30, 4 more patients have been similarly treated. It is obviously impossible to evaluate the results of such treatment in this small group. It appeared, however, that no specific effect could be demonstrated.

Oxygen was administered to 8 patients by tent or mask for varying periods of time with considerable relief of cyanosis and dyspnea. Most of the seriously ill patients were provided with special nursing care which proved very helpful during the height of their illness. Adrenalin was necessary in the few severe cases of asthma which did not respond to ephedrine. As mentioned previously, steam inhalations and cough mixtures were for the most part ineffective, but when sputum production became abundant, postural drainage appeared to be beneficial in some instances. It was felt that a high vitamin, high caloric diet shortened convalescence. This was given as soon as tolerated because considerable weight was lost by most of the patients. Fluids were forced to 3500 ml. *per diem.* and in some cases 4 to 8 gm. of extra salt were added to the diet each day.

TABLE 5.—DURATION OF HOSPITAL STAY IN 40 CASES OF PRIMARY ATYPICAL PNEUMONIA

Days hospitalization	No. patients in given period
5 or less	2
6 to 10	11
11 to 15	13
16 to 34	14

Convalescence. An indication of the duration of illness is given by a tabulation of the length of hospital stay.

The days from work lost by 39 patients* with pneumonia totaled approximately 1000. (These included the days lost prior to admission to the hospital.) The average interval from admission to the date of return to work was 23 days. The period of convalescence averaged 17 days as measured from the termination of fever to the resumption of active duties. It should be pointed out, however, that some of the patients had a very mild attack of the disease, and that some of the most severely ill patients started back to work on a part-time basis. A better concept of extent of convalescence can be obtained from Table 6.

TABLE 6.—DURATION OF CONVALESCENCE IN 39 CASES† OF PRIMARY ATYPICAL PNEUMONIA

Length of convalescence	No. patients† in given period
10 days or less	4
11 to 15 days .	18
16 to 20 days	8
21 to 41 days . .	. 9

During convalescence, 12 persons suffered varying degrees of mental depression lasting from 3 to 21 days, or an average of 12 days. Throughout the early part of convalescence, all but 2 of the 40 patients complained of marked asthenia and easy fatigability which was considered more severe than that ordinarily noted after pneumococcal pneumonia. Only 2 patients had what might be considered relapses during late convalescence.

Epidemiology.‡ Every medical student was interviewed and careful histories of respiratory illness were obtained for the 8-week period ending August 20. This brought to light a few cases of pneumonia that might otherwise have been missed because they had not been hospitalized. In addition a survey was made of the non-student household contacts of students who lived in their own homes or with private families.§ Throughout the epidemic and for several months thereafter, all cases admitted to the hospital, both from the institutional personnel and from the outside community, were tabulated according to date of onset and date of hospitalization respectively. The first and most important fact disclosed by these investigations was that many of the cases in the student body were probably infected through contact with a laboratory instructor in Anatomy and Histology. He became ill July 18, but at that time the medical staff was not alert to the possibility of atypical pneumonia occurring in the school, and this case was missed. As he was permitted for 16 days to continue his work while

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* One patient with rheumatic heart disease is excluded from this tabulation because he was advised to leave medical school for the remainder of the academic year.

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‡ Seven cases occurred among staff and students who were not admitted to the hospital and thus were not included in the description of clinical features. The history and clinical picture in these cases was such as to leave little doubt that they suffered from the same illness and they, therefore, are included in the epidemiologic report. Six cases which were hospitalized after September 30 also are included.

§ Since there are no dormitories or fraternity houses, all students live in private homes.

ill with a severe cough, all members of the first-year class were thus subjected to intimate and prolonged exposure. Under these conditions the disease seems to be highly communicable.

Chronologic Distribution of Cases. A comparison of the chronologic distribution of cases among 1238 members of the institutional personnel with that among other persons in the community is shown in Figure 1. Of the 34 cases occurring in the student body during the last 6 months of 1942, 28 had the onset of their illness during the first 3 weeks of August, and of these 28 persons, 16 were members of the first-year class. Since the incubation period of this disease is estimated to be from 10 to 25 days by most observers, it is possible that many of the students who became ill during August contracted their infection from the
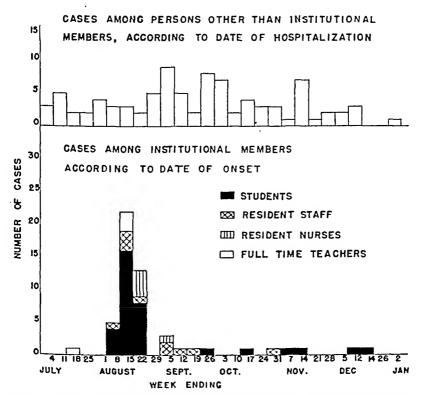
FIG. 1.—Chronologic distribution of cases of primary atypical pneumonia.

laboratory instructor whose illness began July 18. The fact that this instructor's most intimate contacts were with the first-year class lends further support to this possibility. It can also be seen from Figure 1 that relatively few cases among institutional members occurred after the month of August, although admissions from the community at large provided a rather constant source of exposure for resident and nursing staffs and upper-class students.

Distributions of Cases in Subdivisions of Institutional Personnel. In Table 7 is shown the incidence of pneumonia in various subdivisions of the hospital and medical school personnel. The absence of cases among employees and non-resident nurses may be more apparent than real since these groups are not served by the hospital medical service.

and these cases, therefore, might not be reported. If these groups are excluded from consideration, the incidence in students, resident nurses and staff and full-time teachers was 8.45%.

The outbreak rapidly assumed striking proportions chiefly in the first-year class where the total incidence was 18 cases or 26.9%. As related above, 16 of these 18 cases developed during the first 3 weeks in August (in fact, from August 7 to 18) and seem to have been caused for the most part by the laboratory instructor. Among the resident and nursing staffs and the upper-class students working with hospital patients, the incidence was much lower, as noted in Table 7, and there was a distinct tendency for cases to occur in those who cared for patients with atypical pneumonia.

TABLE 7.—INCIDENCE OF PRIMARY ATYPICAL PNEUMONIA IN VARIOUS GROUPS
JULY 7, 1942–JANUARY 2, 1943

Group	Total	No. cases	% ill
First-year students	67	18	26.9
Second-year students	63	7	11.1
Third-year students	60	6	10.0
Fourth-year students	55	3	5.5
Resident staff	65	10	15.4
Resident nurses	185	5	2.7
Full-time teachers	132	4	3.0
Non-resident nurses	155	0	
Employees	456	0	
Totals	1238	53	4.27

Contagiousness of the Disease. As mentioned previously, a survey was made of the non-student household contacts of students in an effort to evaluate the communicability of cases and the possibility that other respiratory illnesses might be subclinical cases capable of transmitting the disease. The results shown in Table 8 are for 402 such contacts interviewed in the period September 6 to 9, about 3 weeks after the occurrence of the majority of cases in the student body. The respiratory infections are divided into pneumonia, simple upper respiratory infections (URI) and respiratory illnesses with constitutional symptoms (suspicious).

Of these 402 contacts none developed pneumonia, even though 46 had been living in the same house with pneumonia patients. Of the 45 contacts of students who had illnesses regarded as suggestive of atypical pneumonia, only a single suspicious case was uncovered. In the group of 200 contacts of students who had not been ill, another suspicious case was found. The only statistically significant increase in incidence of disease (15% of 111 contacts) consisted of simple upper respiratory infections in the group exposed to such infections. This suggests that under the conditions of contact described, the agent of atypical pneumonia is not highly communicable, nor is there an increased frequency of apparently related (suspicious) infections.

Means of Spread of the Disease. Dingle et al.[4] have suggested that inapparent cases act as a reservoir for the spread of the infection. Accordingly, an attempt was made to determine whether the chief means of spread of the agent of atypical pneumonia in this outbreak

was through clinically recognizable cases, or through subclinical cases and carriers. It is apparent that a majority, and possibly all of the cases in the first-year class, could be fairly attributed to the instructor as previously explained. It has also been stated above that among the resident and nursing staffs and upper-class students the majority of cases occurred in those who cared for patients with atypical pneumonia. However, the whole picture was overlaid and confused by the many opportunities for casual contact and by the fact that early in the outbreak cases were not recognized and isolated promptly. Although carriers and subclinical cases may occur, it can be stated that it is not necessary to postulate their existence to explain the spread of the disease in this outbreak.

TABLE 8.—DEVELOPMENT OF RESPIRATORY ILLNESS AMONG NON-STUDENT HOUSEHOLD CONTACTS OF STUDENTS WITHIN A SUBSEQUENT PERIOD OF 3 OR MORE WEEKS

Status of student member	No. contacts interviewed	Non-student household contacts of given groups of students					
		Upper resp. infec.		Suspicious		Pneumonia	
		No. cases	%	No. cases	%	No. cases	%
Not ill	200	16	8.0	1	0 5	0	
Upper resp. infec.	111	17	15.3	0	..	0	
Suspicious	45	3	6.7	1	2.2	0	
Pneumonia	46	1	2.3	0	..	0	
Totals	402	37	9.2	2	0.5	0	

Control Measures. When 18 students had become ill with atypical pneumonia by August 13, measures were instituted immediately to prevent exposure and to secure prompt detection and isolation of cases. It was decided to discontinue classes for the first- and second-year groups and all formal instruction for the third- and fourth-year students. Classes were resumed August 22. For a period of 6 weeks thereafter, each student was required to record his temperature at 8:30 A.M. and 4 P.M. and to report daily for nose and throat inspection. Opportunities for intimate exposure among members of the first-year class were reduced by doubling the number of laboratory sessions and increasing laboratory space to provide adequate separation of students.

Throughout the institution it was repeatedly urged that all illnesses be reported promptly to the medical service. Persons with respiratory illness and fever or constitutional symptoms were isolated until chest roentgenographs and their subsequent course indicated that they did not have pneumonia. In selecting members of the personnel for isolation, much greater significance was attached to sore throat and aching than to coryza, as explained previously. These measures were considered to be successful for the only cases that occurred thereafter were among those who came in close contact with hospital patients suffering from this disease.

Discussion. The observations presented in this paper make it apparent that the outbreak described was one of primary atypical pneumonia in a relatively closed group. But even though the disease was observed under optimal conditions, certain diagnostic difficulties and other clinical problems arose which deserve further comment.

Diagnostic Difficulties. On the basis of the observations described here and elsewhere[3,4,6,9–12,13,14] it is apparent that primary atypical pneumonia is a clinical entity. Worthy of emphasis, particularly in interepidemic periods, diagnosis is difficult clinically and, therefore, careful bacteriologic studies are needed so as to exclude such diseases as tuberculosis, brucellosis, tularemia, typhoid and paratyphoid fevers, sepsis, and atypical pneumococcal pneumonia. Because atypical pneumonia is very readily confused with tuberculosis clinically and roentgenographically, it is essential to search for tubercle bacilli routinely in all cases.

In recent years physicians have acknowledged the importance of routine blood cultures in cases of pneumococcal pneumonia as a guide in diagnosis, treatment and prognosis. Of equal importance perhaps is the need for routine blood cultures in all suspected cases of atypical pneumonia, for the diagnosis can never be made with any degree of certainty in the absence of a negative blood culture.

Dingle *et al.*[4] have reported negative results with sheep-cell agglutination tests in sera from patients with atypical pneumonia. However, as previously stated in this paper, 5 of 11 patients, whose admission sera were negative, developed sheep-cell agglutinins during convalescence. It is necessary, therefore, that additional sheep-cell agglutination tests, including agglutinin absorption studies, be done with serum from patients with this disease.

Another point worthy of investigation because of its unknown significance is the development of "cold" agglutinins in persons suffering from primary atypical pneumonia. Since Peterson, Ham and Finland[13] have found that "cold" agglutinins are present in the sera of the great majority of patients at or near the end of the febrile period, and since trypanosomiasis is the only other infectious disease in which these agglutinins develop regularly, it is suggested by them that their presence may serve as a diagnostic criterion.

Even if the etiologic agent of atypical pneumonia could be isolated with relative ease, virus studies are of limited value as a diagnostic measure in the ordinary hospital laboratory. The difficulties encountered in the isolation of an etiologic agent from patients with this disease are better understood in the light of the recent report by Horsfall and his co-workers[7] which indicates that at least some of the cases have been caused by a virus that is either identical with or closely related to the mongoose infectious virus isolated by Weir and Horsfall[17] in 1939.

The literature contains numerous references to the clinical and pathologic similarity of atypical pneumonia and psittacosis (also ornithosis). In an attempt to bring out some of the important differential characteristics, the outstanding clinical features of pneumococcal, atypical and influenzal pneumonias and psittacosis have been tabulated (Table 9). Perusal of this table and that presented by Goodrich and Bradford indicates that atypical pneumonia and psittacosis occupy a more or less intermediate position between pneumococcal and influenzal pneumonias.

TABLE 9.—DIFFERENTIAL DIAGNOSIS OF 4 TYPES OF PNEUMONIA*

	Pneumococcal	Atypical	Psittacotic	Influenzal
Onset	Abrupt	Insidious	Abrupt	→Same
Cough	Loose	Dry and disturbing	→Same	Loose
Chills	1 or 2	Chilliness or repeated chills	→Same	→Same
Pain	Pleural	Head and tracheal	→Same	Bone, muscle
Fever	Sustained	Hectic	Sustained	Remittent
Pulse	Rapid	Relatively slow	→Same	→Same
Respirations	Rapid	Only slightly increased	→Same	→Same
W.B.C. count	High	Normal in early stages	→Same	Low
Sputum	Rusty	Scanty and tenacious	→Same	Bloody
Convalescence	Short	Prolonged with asthenia and depression	→Same	→Same

* Many important qualifying phrases have been omitted for the sake of brevity.

Interpretation of Leukocyte Response. As previously mentioned, white blood counts ranging from 12,000 to 20,000 cells per c.mm. were recorded during or soon after the period of lysis in 11 severely ill patients. Although a similar degree of delayed leukocytosis has been noted by others,[3,6,9,11,15] this feature of the disease has never been emphasized. Its proper interpretation is obviously a matter of considerable importance because one is tempted to assume that it is an indication of secondary bacterial invasion and to institute sulfonamide therapy on the basis of this assumption. However, most observers agree that complications are rare and it has actually been suggested[9] that this disease increases host resistance to bacterial infection. On the other hand, Rhoads[14] is of the opinion that bacterial complications are more frequent and important than previously realized and that the routine use of sulfonamide is probably justified.

In only 4 of the 40 patients under consideration was there any suggestion of bacterial infection to account for the delayed leukocytosis. One had acute otitis media which cleared without myringotomy, and as previously mentioned, 3 patients had appreciable numbers of colonies of beta-hemolytic streptococci in their throat cultures. In addition, a number of patients developed laryngitis at about the time of the maximal leukocyte response, but laryngeal cultures were not taken. The few colonies of staphylococci and higher type pneumococci isolated by culturing the flora of the throat and sputum during the period of leukocytosis can probably be regarded as insignificant according to the criteria presented by Finland.[5] Moreover, it was observed that most of the patients appeared to be over the critical phase of the illness at the time when leukocytosis developed and that sulfadiazine seemed to exert no specific effect at this stage. It is our opinion that the delayed increase in the number of white blood cells does not indicate, in most instances, the presence of bacterial complications and that it, therefore, might be considered a response to the primary infection, or in other words a part of the natural course of the disease. Stephens[16] has shown that a marked stimulation of the myeloid bone marrow elements occurs during resolution of pneumococcal pneumonia and he has suggested that this might be due to liberation of nucleoproteins. Perhaps the resolution of atypical pneumonia has a similar effect upon the marrow.

As the significance of the delayed leukocytosis in this disease has not been explained by any of the studies reported to date, it is suggested that repeated cultures be taken of all possible foci of infection and that repeated Schilling differential counts and blood uric acid determinations be made in an attempt to clarify this problem.

Sulfonamide Therapy. During the outbreak described sulfadiazine was given to 16 of the 40 patients in adequate, controlled dosages, but did not appear to alter the course of their illness. Although this has been the experience of many others, there remains some difference of opinion regarding future policy with reference to sulfonamide therapy in this disease. Granted that chemotherapy is ineffective against the primary (probably virus) infection, one is still faced with two further considerations:

1. *When the patient is first seen* the diagnosis can almost never be made with certainty. For this reason there is a definite obligation to administer sulfonamide to severely ill patients while awaiting the outcome of bacteriologic studies. If these studies are not indicative of bacterial pneumonia, sepsis or other infection known to respond to chemotherapy and the patient's course and Roentgen rays point to atypical pneumonia, it is desirable to discontinue the drug promptly. This suggestion conforms with that of Janeway[8] who has emphasized that in the treatment of most acute infections it is best to give full doses of sulfonamide from the start and to discontinue them abruptly within 3 days if no response can be achieved, or if a diagnosis of sulfonamide-resistant disease (such as typhoid fever or atypical pneumonia) can be established. When one first sees a less severely ill patient with probable "atypical" pneumonia, there appears to be considerable justification for withholding chemotherapy. In this situation, as in many others, the physician must weigh the probable effectiveness of the drug on the one hand and the possible toxic reactions on the other.

2. *Later in the course of the illness* the question of sulfonamide therapy again presents itself if the patient has (*a*) delayed leukocytosis as previously discussed; (*b*) secondary rise in temperature with or without other clinical suggestion of relapse; or (*c*) frank, clinical relapse. Under any circumstances, the decision regarding chemotherapy depends upon the results of complete bacteriologic studies and upon the judgment and previous experience of the attending physician. In our experience administration of sulfonamide late in the course of the illness is seldom justified.

"Immune" Transfusions. As previously described, 12 patients were given transfusions of plasma or whole blood from convalescent donors without any definite response. A number of other observers have reported similar experience with 1 or 2 patients each. As a result of these combined observations it appears that such transfusions cannot be expected to have any specific effect on the course of the disease. If transfusions are indicated as a general supportive measure, it would seem more judicious to exempt a recent patient who is in the midst of a long convalescence and to draw the blood from a healthy donor.

Conclusions. 1. Primary atypical pneumonia is a disease difficult to diagnose on clinical and epidemiologic grounds and therefore a "missed case" may be of great importance in its spread.

2. Infection usually produces a characteristic clinical picture, but this can easily be confused with a number of other diseases. A positive diagnosis is finally established only when Roentgen ray examination of the chest reveals typical findings, bacteriologic studies are negative, and the subsequent course of the illness is consistent.

3. Under ordinary conditions of exposure, primary atypical pneumonia is not highly communicable in comparison with the common cold or influenza. If subclinical cases or healthy carriers occur they are probably of minor importance in transmission of the infection.

4. Treatment of primary atypical pneumonia is symptomatic only. Sulfonamide therapy is ineffective against the primary (probably virus) infection, but because of diagnostic difficulties, its temporary use in full doses is obligatory in seriously ill patients until bacterial pneumonia, sepsis and other infections responding to chemotherapy can be excluded. The use of sulfonamide therapy later in the disease depends upon the nature of complications, which fortunately are rare, and is influenced by the interpretation placed upon the rising leukocyte count—a feature of this disease which has often been observed but to date has been inadequately studied. Transfusions of whole blood or plasma from convalescent donors appear to have no specific effect.

REFERENCES

1. BARNETT, C. W.: J. Clin. Invest., 12, 77, 1933.
2. BERNSTEIN, A.: Medicine, 19, 85, 1940.
3. DINGLE, J. H., and FINLAND, M.: New England J. Med., 227, 378, 1942.
4. DINGLE, J. H., ABERNETHY, T. J., BADGER, G. F., BUDDINGH, G. J., FELLER, A. E., LANGMUIR, A. D., RUEGSEGGER, J. M., and WOOD, W. B., JR.: War Med., 3, 223, 1943.
5. FINLAND, M.: J. Am. Med. Assn., 120, 1294, 1942.
6. GOODRICH, B. E., and BRADFORD, H. A.: AM. J. MED. SCI., 204, 163, 1942.
7. HORSFALL, F. L., JR., CURNEN, E. C., MIRICK, G. S., THOMAS, L., and ZIEGLER. J. E., JR.: Science, 97, 289, 1943.
8. JANEWAY, C. A.: New England J. Med., 227, 1029, 1942.
9. KNEELAND, Y., and SMETANA, H. F.: Bull. Johns Hopkins Hosp., 67, 229, 1940.
10. KORNBLUM, K., and REIMANN, H. A.: Am. J. Roentgenol., 44, 333, 1940.
11. LONGCOPE, W. T.: Bull. Johns Hopkins Hosp., 67, 268, 1940.
12. McCARTHY, P. V.: Radiology, 40, 344, 1943.
13. PETERSON, O. L., HAM, T. H., and FINLAND, M.: Science, 97, 167, 1943.
14. RHOADS, P. S.: Radiology, 40, 327, 1943.
15. RIVEN, S. S., and STERN, E. A.: South. Med. J., 35, 976, 1942.
16. STEPHENS, D. J.: AM. J. MED. SCI., 188, 332, 1934.
17. WEIR, J. M., and HORSFALL, F. L., JR.: J. Exp. Med., 72, 595, 1940.

PROGRESS

OF

MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF

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GASTRIC DIGESTIVE SECRETIONS IN INFANCY AND CHILDHOOD: A REVIEW

By Irving J. Wolman, M.D.

In adult medicine, gastric analysis is falling into neglect. The great range of normal variations from day to day and from subject to subject, as well as the inconstancy of the secretory patterns in ill-health, frustrates the diagnostic application of the procedure in all diseases except a few varieties such as pernicious anemia and roentgenologically confusing stomach ulcers.[125] Pediatrics has sensed this difficulty, and of late years has directed most of its interest in digestion toward the more fruitful problems of absorption, metabolism and nutrition. The most frequent cause for aspirating children's gastric contents at present is the search for tubercle bacilli. Nevertheless, research in stomach physiology is going on persistently, and fresh studies on gastric function during childhood are constantly being reported.

No broad survey of the secretory responses of the child's stomach has been published since the somewhat limited discussion in Freudenberg's[47] classic monograph on Verdauung im Säuglingsalter, which appeared in 1929. Stewart[134] prepared a list of most of the reports on gastric acidity in health and in anemia published between 1920 and 1934. The present Review is not a comprehensive inventory of all prior articles, but rather a bird's eye summary of current beliefs and problems.

Rennin. *Nature.* Gastric juice of vertebrates, from fish upward, will coagulate cow's milk.[154] With nearly all species the clotting is effected by the pepsin or other proteases present, for most proteoclastic enzymes can cause milk to clot.[110] However, in the case of the calf and the kid but in no other species nor in the adult cow or mature goat — the stomach elaborates an additional powerful milk-clotting enzyme known as rennin.[21] Coagulation in these young animals is useful in impeding the otherwise quick passage of liquid milk into the intestine, in order to hold it in contact with the gastric juices for a long time.

Crude extracts of calf stomach wall rich in rennin are obtainable commercially as liquid rennet, rennet powder and rennet tablets. The dairy industry requires large quantities of liquid rennet to mix with fresh milk in the first stage of manufacture of sundry cheeses. Housewives and

dietitians employ rennet products for making milk foods and flavored sweetened rennet custard desserts. Coagulated rennet custards are useful in the feeding of sick patients and young children as well as of healthy adults, as they make milk more wholesome,[27] are more readily digested[131] and help to augment the daily intake of milk.

Action. Rennin coagulates the colloidal suspension of casein in milk irreversibly. This is regarded as the initial phase in hydrolytic dissociation of the complex protein molecule. vanDam[142a] had stated that lab (rennin) could digest calcium paracaseinate, with the most favorable hydrogen ion concentration being what is now known as pH 5. Later workers (Freudenberg,[41a] Inichoff,[73] Matthiessen,[97a] Willheim[144]) found no increase in amino acid content of various milks by formol titration before and after coagulation with labferment. Current studies,[131] however, are revealing that rennin coagulation is followed by more advanced cleavage of the casein and other proteins, indicating breakdown of some amino acid-carboxyl linkages, though rennet extracts only have been investigated for this behavior and not pure crystalline rennin. Traces of pepsin in the rennin-containing materials tested could cause the weak proteolysis which has been observed.

The chemistry of milk clotting as induced by rennin is not well understood. The hypothesis of Linderstroem, Lang[88a,b] is the one generally accepted at the present time. According to this, casein as it occurs in its original form in fresh milk exists as a system of three components, one forming a protective colloid for the other two. Rennin attacks the protective colloid, thereby destroying the stability of the whole casein system. As shown by increased sensitivity of the casein to the effects of pH and heat, the colloidal equilibrium becomes disturbed, but precipitation does not ordinarily occur unless ions of calcium or some other earthy alkali are present. With milk itself the content of calcium is more than adequate to permit this second step in the coagulation reaction to take place, th⸗ coagulum receiving the name of calcium paracaseinate. It is not kn⸗ whether coagulation reactions between pepsin, trypsin, papain and ot⸗ proteolytic enzymes and milk are dependent upon the same mechanis⸗ and the identical internal molecular rearrangements as in coagulation rennin from the calf's stomach.

Purification. Fenger,[38] Luers and Bader,[90] Tauber and Kleiner[136a] an⸗ Hankinson and Palmer[54] have attempted to isolate rennin in highl⸗ purified form. The results obtained by these investigators with regar⸗ to the chemical and physical characteristics of the enzyme have been con⸗ flicting and highly contradictory, though all data suggest that the enzyme is either a protein in itself or performs its function in association with protein structures. All preparations displayed a manifold increase in milk-clotting potency when compared with the original gastric extracts while the peptic digestive power became diminished markedly. Thus Hankinson and Palmer's concentrate, obtained from an initial commercial rennet of high strength, showed rennin activity increased 4.55 times but with peptic activity decreased to 6.25% of that of the original extract. Very recently Hankinson[55] reported the isolation of crystalline rennin by a complicated series of "salting out" and dialyzing procedures. The crystals secured were somewhat needle-shaped and contained 1.46% sulfur, no iron, and questionable traces of phosphorus and copper. The isoelectric point was in the zone pH 4.45 to 4.65. The milk-coagulating power was very active. Peptic digestion assays were not carried out, presumably because

of the small amount of crystalline matter available for study. The results of further studies on the exact chemical nature of these crystals are awaited with interest.

It is interesting that rennin as withdrawn from the fourth stomach of the calf exists partly in the inactive precursor pro-rennin phase and partly in the activated form as a consequence of contact with the acid component of the secretion. A slightly acid reaction converts pro-rennin to rennin, the optimum circumstance for this process being pH 5.25.

Measurement of Activity. Rennin strength is measured and expressed in terms of milk-clotting power. For instance, 1 part of Luers and Bader's refined dry substance coagulated 16,440,000 parts of reconstituted milk substrate. Many variations in the technique of performance of this test have been proposed. In Tauber's[135] experience, best results are obtained when an equal volume of molar acetate buffer of pH 5 is added to the milk substrate, thus correcting for variations in pH intrinsic to different batches of cow's milk. Tauber sets up a series of test tubes containing 10 cc. of buffered milk at room temperature and varying amounts of the enzyme solution to be tested. The amount of enzyme which causes a clot in 10 minutes is taken as the measure of the potency of the specimen. However, as Hankinson and Palmer[54] point out, the relative milk coagulating activity of rennins obtained at different times by different investigators cannot be compared in exact quantitative terms. Not only do substrates vary but precise optimum conditions are usually not determined with respect to either the specimens of milk used or the relationships between Ca ions and pH, factors which affect the rapidity of coagulation and its completeness. Attempted comparisons are complicated further by the presence of contaminating pepsin, for which optimal conditions differ also.

Absence From Human Stomach. The erroneous concept is widely held among physicians and implicitly subscribed to in many textbooks that the milk-clotting action of human gastric juice is a function of contained rennin. As a matter of fact, however, that human gastric glands are able to elaborate true rennin has never been demonstrated. Gastric pepsin, and not a second ferment rennin, seems to be the agent responsible for the coagulation of ingested milk. Pepsin coagulates milk in the same manner as does rennin. Pepsin gives rise to clots and curds which cannot be distinguished by size and consistency from those produced by rennin,[131] in the pH range in which the latter is active.

The evidence which indicates that the human stomach does not secrete true rennin may be summarized as follows:

(*a*) Numerical expressions for proteolysis and coagulating strength of human gastric juice bear a reasonably constant ratio or quotient to each other.[3,68] This ratio is the same for different individuals as well as for infants, children and adults.[4] Chemical manipulations or heat, when so applied as to partially destroy or inhibit enzyme activity, interferes with both enzymatic manifestations to a parallel degree; the pepsin/rennin ratio does not alter as it should if two separate enzymes were present in the specimen, one a little more sensitive to destructive influences than the other.[65] It is possible, on the other hand, with extracts from the fourth stomach of the calf, to separate a coagulating fraction from a digestive fraction by precipitation with magnesium carbonate. This argues for the separate existence of both pepsin and rennin in the calf.[22]

(*b*) When solutions of pepsin and rennin are mixed together in the laboratory, it is possible to alter the potency relationship existing between the coagulating and the proteolytic activities by adsorption upon colloidal

suspensions of casein.[4] With human gastric juice, dissociation cannot be effected by this maneuver.

(c) Pepsin will digest and destroy rennin when added to rennin in the presence of acid. Dotti and Kleiner[36] applied this principle to a study of adult human gastric juice, observing that no reductions in milk-clotting potency developed when gastric juice was acidified and incubated at 38° C. for 48 hours. They reasoned that if rennin were present in addition to pepsin the total clotting power would have diminished as a consequence of destruction of the rennin by the pepsin. This conclusion may be criticised on the ground that the coagulating power of pepsin is increased many times faster by increase in acidity than is that of rennin. Therefore it is conceivable that with a mixture of rennin and pepsin in an acid medium any tendency to decrease in clotting power due to digestion of rennin by pepsin might be counterbalanced by the increase in coagulating power of the pepsin due to the increase in the acidity.

(d) Differences in chemical behavior distinguish the two enzymes. The effect of rennin ceases with coagulation of milk, but pepsin continues the hydrolysis far beyond the paracasein stage. Rennin can withstand exposure to pH 9 for a short time whereas weakly alkaline solutions inactivate pepsin very quickly. Contrariwise, strong acids will inactivate rennin but not pepsin. The hydrogen ion concentrations for optimum activity are widely separated, that for rennin being pH 5.35,[92] for pepsin about pH 1.8.[107a]

(e) The preliminary studies of Hankinson[55] on his new crystals indicate, if substantiated, that purified rennin possesses quite a different molecular structure from that of Northrop's[107f] crystal pepsin.

Pepsin. *Crystalline Pepsin and Its Properties.* Schwann as early as 1836 had found and named the proteolytic factor in gastric juice, but it was not until nearly a century later, in 1930, that Northrop[107b,d,e] isolated animal pepsin in crystalline form. Crude extracts of secretory mucosa contain not only true pepsin but also other proteinases among which Brücke pepsin, gelatinase and cathepsin have been isolated and identified (vide infra). Hexahedral crystals of pepsin in apparently pure form can be prepared from extracts of swine and of bovine mucosa. Crystalline pepsin has a high content of tyrosine, dicarboxylic acids and tryptophane, and is destroyed rapidly by dilute alkali. The isoelectric point as measured by cataphoresis lies close to pH 2.7, but in solution this value is even more acid than pH 1. The optimum pH for the proteolytic activity of pepsin is about 1.8 when casein is the substrate; about 2.2 when gelatin or hemoglobin is used.[107a] The molecular weight lies between 25,000 and 40,000. Peptic activity decreases rapidly as the pH number rises from 2 to 7, becoming very weak at pH 4 and completely inhibited by pH 7.[52,60] Neither in morphology nor in rates of digestion of different substrates nor by precipitin tests are the crystals from swine distinguishable from those from bovine juice. The solubilities however are independent and different as are their responses to specific inhibitory substances, suggesting that pepsins vary slightly in structure from species to species as do the hemoglobins. Human pepsin has not been isolated in the crystalline state.

Fruton and Bergmann,[44,45] studying hydrolysis of synthetic peptides by different pepsins, found that the splitting occurs exclusively at the peptide linkages which involve the amino group of the aromatic amino acids. They noted many deviations from the generally accepted optimum of pH 2 for pepsin action on proteins, and concluded that this observed optimum represents the average of the optima for the various peptide linkages

attacked by pepsin. Very recent studies[2,132,133] indicate that Northrop's crystalline preparations are intrinsically a mixture of several component forms of pepsin possessing differing chemical properties.

Physiology of Secretion. Ever since Heidenhain's time, histologists have concluded that the proteinase or pepsin of gastric juice is elaborated by the zymogenic body chief cells of the fundus mucosa.[69,70,87,95] The content of zymogen or pepsinogen granules in the cells is highest when fasting, lowest just after a meal. Proteins are good stimulants of pepsin secretion in dogs, with formation proceeding at a constant rate for some hours. Experimental stimulation of the dog's vagus nerve, which produces a great increase in the pepsin content of the secretion,[17] results also in an extreme discharge of zymogen granules. By contrast, injections of large doses of histamine into dogs with Pavlov pouches or gastric fistulas fail to excite the production of pepsin even though marked increase in acidity becomes evident. In man, interestingly, under the usual conditions of histamine stimulation an increased output of both acid and pepsin[12,59,99,115,116b] may be elicited though the correlation between these two factors is not significant.[116c] Bowie and Vineberg[17] have suggested that this discrepancy between the species is apparent rather than actual or of basic physiologic importance. The flow of stimulated juice may do no more than flush out secretory products already present within ducts and cells.[72] Thus there is no unequivocal proof that humoral stimulation in human beings plays an important rôle in the rate of pepsin production.

Langley[83] in 1882 had noted that a slightly alkaline extract of fresh gastric mucosa contained an inactive substance which was not changed by alkali as is pepsin but which became transformed into pepsin when the solution was acidified. This precursor, *pro-pepsin* or *pepsinogen*, was crystallized finally by Herriott[61] in 1938, who isolated needle-shaped crystals of protein nature which on later acidification and recrystallization yielded another form of crystal identical with Northrop's commercial pepsin. Conversion of pepsinogen to pepsin within the stomach takes place as a spontaneous autocatalytic reaction, accelerated by pepsin itself. Immunologic studies[126] of crystalline pepsin and pepsinogen show them to be immunologically distinct from each other and their homologues of other species, though some cross-reactions do take place.

Northrop's studies have shown that the relative rates with which crystalline pepsin hydrolyzes various proteins in acid media do not differ significantly from the rates exhibited by crude gastric juice. This is taken to mean that the essential proteolytic factor in gastric juice is pepsin. The observations of Freudenberg and Buchs[47] on cathepsin indicate that proteolysis within the human stomach is somewhat more complex.

Measurement of Activity. When a protein solution is acted upon by an enzyme mixture a number of separately distinguishable chemical and physical changes can result. Hence when determining the enzyme potency of an impure preparation, if whether the catalyst present is single or multiple is not known, it is good if feasible to investigate more than one single property of the protein or to measure the activity by means of two or more substrates. In the case of human gastric juice, since the active protease has been believed to consist almost exclusively of pepsin alone, popular usage has considered as adequate for assay of potency any one of the changes this enzyme produces upon a single substrate.

In actual clinical practice dozens of techniques have been employed for the quantitative measurement of peptic strength of gastric juice. The classical Van Slyke[10] amino titration utilizes the special property of nitrous acid to attack free amino groups, liberating nitrogen which can be

caught and measured. Sörensen's[130] formol titration rests upon the tendency of formaldehyde to destroy the alkaline effect of free amino radicles. When a protein disintegrates in the presence of formaldehyde, free carboxyl groups which accumulate can be titrated against standard alkali. Measurement of the milk-clotting strength can be secured with a modified viscosimeter[82] or by direct observation of the specimens.[8,58] This principle is in wide use. Northrop[107c] determined the changes in viscosity of gelatin, casein and edestin colloidal solutions when exposed to pepsin and also ascertained the increase in formation of soluble nitrogen by the micro Kjeldahl apparatus. Manchester[94] took narrow strips of protein made from sheep gut sausage casings or of cooked egg albumen, suspended in pepsin-containing test solutions. A small metal clip was attached to the free end of each strip; the time of breaking was taken as the index of enzyme strength. Bloomfield and Polland[116b] measured disintegration of edestin by gastric juice. Anson and Mirsky[5a,b] developed an excellent though difficult technique for estimation of proteinases, using hemoglobin. Pepsin will attach hemoglobin; the extent of hemoglobin digestion can then be determined by precipitation of the undigested material with trichloracetic acid, and measuring the concentration of soluble amino acids in the filtrate which give a blue color with phenol reagent.[39] This method has been simplified by Beazell et al.[9] for the less sensitive purposes of the physician's laboratory. Gilman and Cowgill[46] proposed the photometric determination of the amount of silver liberated by the digestion of an exposed and developed photographic film; Osterberg, Vanzant and Alvarez[109] found this method very satisfactory. Mett's capillary tubes filled with coagulated egg albumen[100] have been given up by many workers[1] because of uncontrollable inaccuracies inherent in the procedure. There seems to be no need to go further in enumerating the available procedures for estimation of pepsin in gastric juice, especially since such examinations have not proved of much value clinically.

Since there is no rennin in human gastric juice and since coagulating of milk represents the initial stage in the proteolytic digestin of casein by pepsin, the concentration of pepsin may be ascertained by measuring the time required for any given solution to clot milk. The results are compared with control values secured by use of standard pepsin in known dilutions.[8,16d,58,60] For the average physician's office or clinical laboratory lacking special facilities and equipment such simple, rapid methods based upon milk-clotting power are reasonably accurate and easy to work with.

Clinical Observations. Osterberg, Vanzant and Alvarez[109] described the difficulties involved in utilizing pepsin measurement as a clinical tool. Fasting specimens were observed to vary widely, the fasting findings in 24 normal males ranging from 5 to 1930 units (Gilman and Cowgill technique). This extreme variability was ascribed in part to contaminating secretions from saliva and duodenum. More consistent results were obtained following a Ewald type meal, the values ranging from 0 to 580 units. Repeated tests on the same individuals on successive days showed great lack of uniformity. The figures for males averaged higher than for females. These authors concluded that no reading could be termed abnormal unless it lay well beyond the range of normal values.

Studies on adults (S113) have shown that pepsin is frequently recoverable from patients with complete anacidity. Evidently the secretion of gastric enzymes may persist after acid secretion has stopped. In cases of pernicious anemia, cancer of the stomach and severe gastritis, the pepsin output is diminished, often to extremely small amounts.

The presence of a ferment capable of coagulating milk and attacking

egg white in the gastric juice of unfed infants but a few hours old has been detected by many workers.[62,65,117,134,152]   That this enzyme exists in the gastric secretion of infants and children is plainly evident by the curds present in regurgitated milk meals.   Ogilvie,[108] one of the latest workers to study gastric pepsin, determined its content in health, anemia, rheumatic fever, and celiac disease, using the Mett tube method.   The figures obtained showed wide variations, but no instance of deficient pepsin was encountered.   Steimann[133] encountered 1 case of absent pepsin in 100 children examined.   Jacobsen,[74] Chievitz[23] and Muhl[105] have reported instances of full achylia with both pepsin and free acid absent.   Subsequent examinations on these cases were not performed.

For a summary of older observations on pepsin in health and disease, Freudenberg's monograph[42] may be consulted.   The Reviewer has failed to uncover any large series of pepsin determinations on normal growing children, performed by modern reliable methods, to indicate that a differential rate of secretion as related to age takes place with pepsin, similar to that for hydrochloric acid.

All investigators who have studied gastric function in infants with test meals of milk have noted that cow's milk mixtures rarely attain a hydrogen ion concentration lower than pH 4, even after remaining in the stomach for 2 hours or longer.   Breast milk, in contrast, because of its lower buffer capacity in conjunction with the abundant formation of fatty acids from the action of its own lipase, may attain a pH of 3 or lower.   Since, as has been noted, pepsin does not exert any appreciable proteolysis on casein until the pH has dropped below 4, and has maximal action at 1.8, the conclusion seems inescapable that during infancy pepsin contributes little to the breakdown of milk proteins, apart from causing coagulation to take place.   With older children[145] in whom the secretion of acid is more abundant, the pH of ingested milk will ultimately fall below 4, sometimes as low as 2, but only after a significant interval of time has gone by.

Cathepsin.   *Properties.*   In 1940 Freudenberg and Buchs[20,41b,43] announced that the proteolytic enzyme cathepsin, which had been discovered in the intrinsic tissue of the stomach wall by Willstätter and Bamann[146] in 1929, was present in quantity within the gastric secretion.   Cathepsin is an intracellular enzyme recoverable from nearly every body tissue, though most abundant in leukocytes, lymphoid organs, kidneys and liver.   It acts best at pH 4 to 5,[41c] and is inert at neutrality.   Hence, within living cells this substance is probably inactive.   After death, however, as the intracellular hydrogen ion concentration rises through anaerobic production of carbonic, lactic and other acids, the proteolytic effect upon the tissue proteins becomes manifest as a major element in autolysis.[146]   Willstätter had believed that the cathepsin recoverable from the stomach lumen originated in leukocytes migrating from the lymph follicles of the mucosa.   Freudenberg and Buchs on the other hand maintain that cathepsin is a true secretion, pointing out that the rapid rate of its formation and failure to reduce the concentration in fresh juice by centrifuging off the leukocytes permit of no other interpretation.

Significance in Gastric Juice.   For years the workers in the field of infant feeding had been suspicious of the presence of a second proteolytic enzyme in gastric juice, operative at the isoelectric zone of the milk proteins.   Rosenbaum and Spiegel,[121] Mathiesen,[97] R. Hess,[1s] and Budde[17] had all incubated gastric juice with milk under conditions of low hydrogen ion concentration and observed a subsequent increase in soluble nitrogen formation.   This increase could not be explained in terms of pepsin action, since with in vitro studies pepsin proves active only with strong acidities

(pH 1 to 3).   That cathepsin might explain this puzzling phenomenon had been mentioned by Freudenberg as early as 1929,[42] but not until a decade later did he succeed in demonstrating its actual presence in quantity in the gastric juice.

Freudenberg and Buchs[43] studied the proteolytic power of many specimens of gastric contents, comparing digestive strength at pH 2 (optimum for pepsin) with that at pH 4.7 (optimum for cathepsin).   With milk as a substrate, and increase in residual nitrogen in mg. per 100 cc. as the index of activity, these data were obtained:

	Pepsin	Cathepsin
54 infants	46.5±3.26	27.4±2 07
16 older children	99.2±8.90	78.1±6.67

Similar data were secured with a half dozen adults.   With several infants the cathepsin figures exceeded those of pepsin.   In general cathepsin potency seemed to range between 50 and 100% of that of pepsin.   It was noted that more marked digestion seemed to take place with juice from infants being raised on cow milk mixtures than from breast-fed infants.

Differentiation From Pepsin.   Cathepsin was found to be most active at 63° C., a temperature at which pepsin and most biologic ferments are partially destroyed.   At this temperature (63° C.) its digestive potency exceeded that of pepsin at 45° C., which is optimal for the latter.   Hydrogen sulfide augmented cathepsin activity a little.   Following the mixing of gastric juice with a number of different chemicals the toxic effects upon the cathepsin and pepsin components were in some instances parallel, in others divergent.   Cathepsin attacked casein, lactalbumin and egg albumen—true proteins—but had no influence on the several dipeptides tested. Early attempts to separate the gastric juice into two fractions, each containing one of the proteolytic enzymes, were not wholly satisfactory.   Best results were secured by adsorption upon cholesterol.   Very recently, however, Freudenberg[41c] did succeed, by selective precipitation procedures, in obtaining a pepsin-free solution of gastric cathepsin.   The milk coagulating or rennin-like titer of gastric juice specimens was in no way proportional to cathepsin content.   Cathepsin-containing extracts when activated at 37° C. by hydrogen sulfide showed no parallel increase in clotting strength.   Indeed, following warming to 60° C., the clotting power became markedly weakened in spite of the fact that the activity of the proteolytic factor was enhanced by the procedure.   Purified cathepsin-containing preparations exhibited almost no clotting power.   From these findings the authors concluded that curdling of milk in the infant stomach is not accomplished by the cathepsin present.   It was their further belief, based on earlier determinations of gastric acidity during digestion, that much of the proteolysis which does take place in the infant's stomach is effected by cathepsin and not by pepsin.

These observations of Freudenberg and Buchs are new and of fundamental importance if substantiated.   One can expect a wave of new investigations exploring possible application of the cathepsin factor to the many diverse problems of gastro-enterology, especially in the pathogenesis of gastric ulcer.

Minor Proteinases.   *Gelatinase.*   Mention should be made in passing to the recovery by Northrop[107c] of a gelatinase or gelatin-liquefying enzyme from crude preparations of bovine pepsin.   This when isolated as an amorphous powder proved to be about 400 times as active as crystalline pepsin in the liquefaction of gelatin.   In contrast its activity as measured by the digestion of casein, edestin or egg albumen was much less than that of crystalline pepsin.   The presence of such a specific enzyme in

human juice, separate from the pepsin contained therein, has never been explored, probably because sufficiently large quantities of human secretions to yield weighable solid precipitates for the chemist to work with are well-nigh impossible to obtain.

Brücke-pepsin. Kraut and Tria[80] described the recovery from commercial pepsin, by an old method used by Brücke, of a protein-free preparation of non-crystallizable pepsin in addition to Northrop's crystalline form of the enzyme. It has been pointed out[107f] that gelatinase and Brücke-pepsin together represent a relatively negligible part of the total proteolytic activity of crude gastric juice.

Amylase-accelerating Factor. Davison[32b] has called attention to the amylase-accelerating action of gastric contents. The addition of infant gastric contents to fresh hog pancreas extracted in saline solution increased its starch-liquefying activity nearly eight-fold.

Lipase. *Properties.* Not many facts are known about the gastric lipase. Its presence explains the distinctive odor of butyric acid recognizable when vomiting follows milk or any meal containing butter fat. There is some uncertainty as to whether in humans it is secreted directly or enters the stomach by the route of duodenal regurgitation, but Freudenberg[42] and others[10,31,86] who have studied the subject consider that the gastric wall can and does produce a lipolytic enzyme of weak potency. The optimum hydrogen ion concentration for its activity is pH 4-5. Unfed newborns have gastric lipase,[62] and it appears to be constantly present through infancy and childhood.[49a]

Breast Milk Lipase. Freudenberg[42] carried out extensive studies on fat digestion with special attention to breast milk fat. It appears that both breast milk and cow's milk contain a certain amount of natural lipase, which is thermolabile. In the case of cow's milk this enzyme becomes destroyed during pasteurization or boiling. With breast milk, on the other hand, which ordinarily receives no heat treatment in advance of being fed, the contained lipase appears to play an important rôle in the digestive breakdown of fats, acting through several interesting mechanisms. For one thing, the optimal hydrogen ion concentration for breast milk lipase lies between pH 7 and 8; at pH 6 its performance is reduced to one-half; at pH 5 to one-tenth. Regurgitation studies show that with young infants receiving breast milk, which is normally slightly alkaline, the acidity of the gastric contents following nursing does not fall to pH 6 until 30 minutes, and pH 5.5 is not attained until nearly 2 hours. Thus conditions for lipolysis remain favorable long enough for an appreciable fraction of the butter fat to break down. With older infants the more liberal secretion of hydrochloric acid and the fatty acid formation act together to produce conditions of high acidity in the stomach.

Lipokinase. Breast milk when left standing at room temperature for some hours does not grow rancid, yet when mixed with gastric juice becomes rancid immediately. Freudenberg[42] extracted a thermolabile glycerin-soluble lipase-activating agent from the gastric wall of some species of animals and demonstrated the presence of this same agent in human gastric juice both during infancy and throughout life. This he named "lipokinase." The function of the lipokinase is to activate the fat-splitting enzyme which in fresh breast milk occurs in an inactive or "pro-lipase" state.

Hydrochloric Acid. *Physiology of Secretion.* All current work points to the parietal cells as the source of gastric acid.[32,44,66] The histologic evidence[23,44] suggests that these cells secrete an unidentified alkaline or weakly acid chloride compound which hydrolyzes to yield hydrochloric acid as the

secretion wells out of the gastric foveolæ. Biochemical studies, however, indicate that the parietal secretion is formed directly as an isotonic solution of pure hydrochloric acid, with perhaps a little potassium chloride mixed in. One must marvel at the ability of these single cells to alter the concentration of hydrogen ions more than a million times. The negative Cl⁻ ions which accompany the H⁺ ions come from the neutral chlorides of the blood and lymph. This is shown by the lower concentration of chloride ions in the venous output from the stomach when secreting, as compared with the arterial supply tested simultaneously. The reactions which liberate the positive hydrogen ion are very obscure. Many hypotheses have been proposed.[21,53,65c,97] Surface membrane phenomena undoubtedly play an important part. Davenport[30] has suggested that the production of carbonic acid from carbon dioxide and water under the influence of carbonic anhydrase is a necessary intermediate step. Equally obscure is the mystery of the regulation of intensity of acidity within the gastric contents. Rosemann,[121] Katsch et al.,[75] and other workers[93] had contended that the extent to which the stomach converts plasma chlorides to hydrochloric acid depends upon the intensity of the secretory stimulation. However, the theory more widely held, first advanced by Pavlov,[112] is that the gastric hydrochloric acid is secreted from the mucosa glands at a high and more or less constant concentration under both normal and pathologic circumstances, regardless of the *rate* of secretion. Thus Hollander[65a,b] calculated that the parietal secretion of dogs would consist essentially of free hydrochloric acid and water, in a concentration of 165 to 170 mg. per liter, and demonstrated specimens from fundic pouches which were nearly of that strength. Gray[48] confirmed Hollander's figures for chloride, but stated that the parietal secretion consists of 166 mg. per liter of Cl⁻ ion, 159 of H⁺ ion, and 7 of K⁺ ion. Teorell[137] had interpreted the changes in acid buffer solutions introduced into cat stomachs as meaning that the "primary secretion," expressed as hydrochloric acid, was a little less than 208 ± 6 mg. per liter. The figure given by Hollander as representing the approximate concentration of the original acid secretion becomes, when expressed in more familiar terms, 0.6% HCl, with a pH value of 0.87; 100 cc. will be neutralized by about 165 cc. of 0.1 N alkali (165 chemical "units" of acidity).

Acidity-reducing Mechanisms. Regardless of the precise strength of "primary" juice, all workers are agreed that secondary acidity-reducing mechanisms are constantly in action to bring down the acidity strength to the lower, less concentrated values existing within the normal stomach. A number of diverse neutralizing and diluting agents mix with the freshly secreted acid as soon as it reaches the mucosa surface, and perhaps within the orifices of the secretory ducts themselves. A multitude of investigations have been directed towards these various neutralizing mechanisms.[16,65b,72,118,143] Hollander's[65b] review classifies them as follows:

A. Variation in the volume rate of HCl poured into the stomach.
B. Extragastric factors.
   1. Dilution and neutralization by saliva.
   2. Dilution and neutralization by regurgitated duodenal fluid.
   3. Dilution by the test-meal itself (when used).
C. Intragastric factors.
   1. Possible variations in the composition of the parietal secretion itself.
   2. Reabsorption of HCl, already secreted, by the gastric mucosa.
   3. Dilution by the peptic secretion.
   4. Dilution and neutralization by a distinct dilution secretion.
   5. Dilution and neutralization effects of mucus secretion from the surface epithelium.

The control, characteristics and individual importance of these factors are far from constant, varying from person to person, and even in the same individual from moment to moment. Thus, the stomach when fasting or after simple stimulation contains a composite mixture of fluids. The strength or concentration of hydrochloric acid found at any random aspiration represents the resultant of a whole series of secretory phenomena, with fluctuant components which are never constant or stable.

The bulk of the studies on gastric acid control have been carried out on experimental animals and adult human subjects. No peculiar physiologic mechanisms beyond what are known or presumed to be true for adults have been demonstrated as being operative in the pediatric age period, although the strength of acid secreted is much less in childhood than in maturity.

Purpose of Gastric Analysis. Since secretion of acid is one of the obvious major functions of the stomach, and readily determinable by simple testing, clinicians from the time of Beaumont have been measuring and recording the stomach's hydrochloric acid content in a host of normal and abnormal conditions, hoping to find in the readings a major index or criterion of the efficiency of its work. Repeated fractional examinations following simple test meals are considered by many workers to be more informative than single specimen diagnostic aspirations. Innovations and minor changes have been and are still being introduced.

Hollander and Penner[67] have reviewed the whole field of gastric analysis from the viewpoints of history, development and usefulness. Their criticisms of acidity determinations are representative in general, though perhaps not in every detail, with the experienced judgment of modern gastro-enterology, and merit the following brief summary: Single specimens of acid containing gastric juice withdrawn after any of the test meals rarely yield pathognomonic diagnostic information. Nor does the fractional method adequately fulfill the hoped-for purpose of demonstrating pathologic variations in the ability of diseased mucosa to respond to a standard stimulus. So-called "normal" curves can occur in the presence of obvious stomach disease, whereas "abnormal" curves are not uncommon among healthy individuals. Wide day-to-day variations may occur in the fractional curves obtained with any one individual with or without gastric disease. For these reasons, in addition to others concerned with details in performance of the acidity tests themselves, many physicians and institutions "have accorded to gastric analysis a forthright negation of all but a modicum of diagnostic significance." There is great need to develop and standardize all the physiologic procedures which show promise of value, and to apply the principle of fractional analysis to the study of the many individual physiologic components of gastric behavior.

Titration of Acidity. Töpfer's quantitative procedure is the technique most widely used for measurement of gastric hydrochloric acid. Ten cc. of filtered gastric juice is mixed with 3 or 4 drops of dimethylaminoazobenzol (0.5% alcoholic solution) and 3 or 4 drops of phenolphthalein (1% alcoholic solution) in a porcelain dish. N/10 NaOH is then added drop by drop from a burette until the last trace of red color disappears. This reading is noted. Titration is then continued further until the red tint of phenolphthalein has reached a maximum. The number of cc. of NaOH solution calculated to produce the first color change in 100 cc. of gastric juice is taken as the measure of free acidity. That figure was often expressed as clinical "units" and frequently written with the degree sign (°). This old system of representing gastric acidity values is being replaced rapidly by the standard notation of modern chemistry. Readings are given in terms of or millinormal terms, abbreviated as N or mN respectively. Fortunately, the

numerical representation is the same, whether the unit of acidity be "degrees" or mN. The number of cc. of NaOH which would produce the second color change in 100 cc. of gastric juice similarly represents total acidity. In the present Review, for reasons of brevity, the figures will be used alone without any descriptive designation. The term "free acid" refers to the hydrogen ions not linked to the buffer substances. The "total acid" is a measure of the free acid plus the entire buffer capacity to the end-point of phenolphthalein.

Several criticisms of Töpfer's method are pertinent. Gastric juice is a buffered mixture of assorted gastro-intestinal secretions. As Michaelis first pointed out,[102] titration to the full yellow color of dimethylamino-azo-benzol corresponds to a pH value of 4 to 5. It gives therefore a misleading end-point for free HCl, which falls at pH 2.8. In the pH range 3 to 3.8 neutralization of the acid proteins and the phosphates of the secretion account for much of the "combined acidity" once attributed to bound HCl.[96] Moreover the red color of phenophthalein marks a pH of 8 to 10, a reaction much more alkaline than that of the blood serum from which the acid digestive juice was derived. The indicator thymol blue would be preferable since it possesses a considerable higher degree of chemical and physiologic accuracy for free and total acidity.[127] Unfortunately the conventional method of scoring in gastric analysis carries such a weight of tradition and already accumulated data that most contemporary workers, such as Cutter,[28] are impelled to continue with it, though fully cognizant of the defects.

Total Chlorides. The total chlorides of gastric contents consist not only of secreted hydrochloric acid and its salts, but also of neutral chloride derived from the alkaline secretions of fundus and antrum, from saliva, and from regurgitated duodenal fluid. It might be anticipated that study of the balance between free and total chloride would throw light on the relative importance of the various factors in secretion, but attempts to relate changes in chloride concentration with disturbances in secretion have not proved successful. Data on total chlorides can be found in many reports[35,37,108] and have been especially investigated in children by Copeman and Hill.[26]

The Resting Secretion. Fasting secretions, collected after no food or drink has been taken for 8 to 12 hours, show extreme variability in content of all elements.[148] Single specimens are wholly unreliable as indicators of the state of secretory function.

Test Meals. MILK. A variety of foodstuffs and other substances have been proposed as standard test stimuli of gastric secretion. With infants, and with older children as well, the customary milk feeding mixture or some other related meal which the child has been taking regularly would seem the reasonable stimulus to use, for then one would get a true picture of what goes on inside the stomach during the every-day pattern of digestion. Indeed, ordinary milk meals were given for this purpose by the early students of childhood digestion, whose roster included the names of Kronenberg,[81] R. Hess,[63a] Hahn,[50] Davidsohn,[31a] Babbott *et al.*,[6] Davison,[32a] Marriott and Davison,[95] Yllpö,[151] Wills and Paterson,[145] Griswold and Shohl,[49] Parsons,[111] Demuth,[54] Klumpp and Bowie,[77] Klumpp and Neal,[75] Banu, Negresco and Heresco,[7] and Gianni.[49a]

Milk is not the best standard test meal because its buffer strength fluctuates with season of the year, breed of the cow, extent of dilution and precipitation in the formula, and size of the curds which form in the stomach.

The buffer value of cow's milk, plain or modified, is so great that the

acid free in the stomach at the moment of drinking becomes obliterated, absorbed by the buffer. For the first few minutes following ingestion, therefore, the pH of the gastric contents are essentially the same as the pH of the milk itself.[145] The pH then begins to fall slowly as the digestive secretions start pouring out. Coagulation of the milk soon takes place, complicating the chemical picture. Boluses of milk are intermittently spilling out into the duodenum at inconstant and unknown rates, further clouding the interpretation of the findings. As the consequence of the interaction of all these complex factors the slope of the pH curve given by successive samples of a milk meal withdrawn at regular intervals represents the resultant of a multiple series of changes rather than a pure secretory response.

Many valuable data helpful to an understanding of the function of the stomach as a digestive organ have been yielded by the withdrawal of milk meals subsequent to feeding. However, to analyze the rôle played by the stomach as a unit in the child's digestive system lies outside the scope of this Review, which is being confined to a study of the secretions themselves. Yet, by way of illustration, one table of data, that of Marriott and Davison,[95] is given here to show the sort of information that may be secured. Specimens were withdrawn 2 hours after feeding. The figures represent the pH of gastric contents of normal infants compared with others suffering from infectious or nutritional disturbances.

	Breast milk	Cow's milk	Lactic acid milk
Normal	3 75	5 10	3 71
Abnormal	4 74	5 35	4 10

When fever is present, acid secretion fails (vide infra). This agency may account for the above differences.

BARLEY GRUEL was preferred for testing of sick and well infants by both Meyer[101] and Chievitz[23] who reported as follows: infants secrete less acid than older children; wide variations occur within each age group and with individual children; infants being raised on milk-free or milk-poor diets secrete as much acid as those receiving abundant milk; infants with acute parenteral infections may have decreased acidity for some weeks thereafter; in chronic gastro-intestinal disorders free acid may be low or absent. Chievitz found not one single instance of achylia in 53 infants examined.

With older children the EWALD TYPE OF TEST MEAL, consisting of roll, toast, shredded wheat, arrowroot cookies or cooked cereal with water or unsweetened tea, was used to obtain the data on normals presented by Hurwitz,[71] Sauer et al.,[124] Klementeson,[?] Copeman and Hill,[?] Wright et al.,[150] Wright,[149] Dietrich and Shelby,[35] and Vanzant et al.[143] The Ewald test breakfast is taken on an empty stomach after an overnight fast, and the contents removed by aspiration 1 hour after the start of the meal. The data in Table I were secured by this method.

The ALCOHOL MEAL, consisting of 50 cc. of 7% grain alcohol injected through a small tube, has received attention because the returned material is watery and easily removed (Ogilvie,[113] Stewart[139]). Steinmann[133] considered a 0.05% caffein solution equally effective. With either the Ewald or the alcohol meal "fractional" removal of gastric contents can be practised, specimens being withdrawn for testing every 10 or 15 minutes and the acidity changes followed until they return to the original fasting level.

Dietrich and Shelby[35] compared the shredded wheat and alcohol test meals in a small group of 14 children, using histamine also. It was noted that the Ewald test meal substances plugged the stomach tubes and hampered the laboratory titrations, besides being contaminated with saliva. The alcoholic solution was free from these handicaps, but was thought to represent an unusual unfamiliar stimulus to a child. Histamine produced satisfactory specimens and was of great aid in distinguishing between true and false achlorhydria. Their average values were: (a) 1 hour after Ewald meal, free acid 22.2, total acid 43.2; (b) 30 minutes after alcohol meal, free 50.3, total 71; (c) 30 minutes after histamine, free 89, total 114.1. Alcohol is a stronger stimulant than a carbohydrate meal, and histamine is much more powerful than either. The authors concluded that the figures for free hydrochloric acid and total acidity for healthy children present such wide variations that a normal figure cannot be stated.

The absence of any unanimity among the experts as to which type of test meal stimulus can be considered most suitable as a test for gastric functioning efficiency suggests that none of the meals fulfills the desired purpose adequately. For a more complete discussion of relative merits and faults, and details as to administration, the reader is referred to standard texts (e. g., Ref. 139), and to the critical review of Hollander and Penner.[67]

Stimulation With Histamine. RESPONSE. The stomach reacts to a parenteral injection of histamine with an extreme secretion of acid. The maximum volume, maximum free acidity, maximum total acidity, and, least reliably, lowest pH number may all be measured as significant indicators of secretory strength. These factors all pass their height and subside before an hour, usually attaining highest values at about 30 minutes. Bloomfield and Polland[13] claim that repeated examinations in the same adult subject following any given dose of histamine will yield secretion curves closely resembling each other. Most workers with children have assumed that this generalization, which is based upon adult material, holds equally well with youthful subjects. Cutter[28] found that with co-operative children repeated testing over several days produced moderate variations in the fractional curves, but when a state of anger or terror persisted through the test the results were erratic and as a rule in the direction of decrease in acidity. This failure of the powerful stimulant histamine to overcome the inhibitory influence of the psychic state upon gastric acid secretion is a telling illustration of the extensive control which emotions mediate on digestion.

DOSAGE. With children, as with adults,[47] the response to histamine has been found to be dependent upon the size of the dose.[28,55,105,125] A small dose will evoke a small quantity of less concentrated juice. For clinical testing of stomach function the consensus has been to employ a dosage large enough to produce hyperemia of the skin and slight accelera-tion of the pulse rate, without more toxic symptoms of headache or collapse. The careful studies of Dietrich and Shelby,[35] Siemsen[125] and Cutter[28] indicate that 0.01 mg. of active histamine per 1 kg. body may be recommended as the optimal dosage for children of any age. In ad-ministering histamine this dosage should be calculated in terms of the amount of histamine base present in the preparation being given; e. g., histamine dihydrochloride contains 60% histamine base whereas ergamine acid phosphate consists of but 36% of active substance. When perform-ing the test it is customary to remove the gastric contents fractionally

every 10 or 15 minutes for $\frac{3}{4}$ to 1 hour while the gastric catheter rests in place. In actual performance, specimens which by a yellow color suggest contamination with regurgitated duodenal juice are discarded. The marked increase in gastric acidity which follows histamine shows that no large amount of alkaline saliva[32a] is being swallowed during the test.

NORMAL VALUES. It is not feasible or necessary to reproduce all minutiae of the accumulated data on the results of the histamine test with children.[25,28,37,56,76,105,123] The reported observations indicate that for children, as with adults, an extremely wide range of variation can be found among individuals of the same age and state of health. The volume of stimulated gastric secretion increases in proportion to body growth as expressed by weight. The mean concentrations of acid do not increase in any such parallel proportion. Strong values for hydrogen ion concentration are attained soon after 1 year of age.

The wide scatter of the data, the limited number of observations, and the dissimilarities in technique and presentation used by the different authors make it difficult to compile an elaborate statistical presentation of normal values for histamine-stimulated juice. The following table is compiled from the sources cited. It shows the range of spread reported for healthy American children. Approximately 0.01 mg. histamine base per kilo was given. The data for secretory volume have been recalculated in terms of cc. per minute in order to get a common denominator for comparison.

Age	Secretory volume (per minute) (cc.)	Free acidity	Total acidity	pH
Prematures	0 12-0.15	0	0- 8	4 7
Newborns	0 20-0 45	0- 20	15- 40	2 3-3 6
2 wks. to 6 mos.	0 25-1.10	0- 59	5- 71	1 5-3 4
7th to 12 mo.	0 40-1.50	12- 80	25-105	1 5-2 2
1 to 2 yrs.	0 70-1.80	15- 95	26-106	1 2-2 0
2 to 5 yrs.	0 50-2 20	29- 90	38-102	1 4-2 0
5 to 10 yrs.	0 10-3 30	53-113	61 145	1 4-2 0
10 to 15 yrs.	2 70-3 60	49 115	61 128	1 4-2 0

As a comparison, the range in total acidity for normal adults as observed by Bloomfield and Polland[152] had extended from 30 to 150 after histamine stimulation. Three-fourths of the values were over 100 and the greatest number of cases were encountered at about the 135 range.

SIGNIFICANCE IN ANACIDITY. In Dietrich and Shelby's[25] comparison of healthy children one interesting 6 year old child gave weak juice with the Ewald and alcohol test meals, the highest readings being 13 for free HCl and 32 for total acid obtained with the Ewald meal. Later, after 0.25 mg. of histamine (0.01 mg. [kilo] body weight) a rise to 105 free HCl and 115 total acid was secured. This case illustrates the universal experience that histamine stimulation should be employed with every patient who shows low secretion of acid with a test meal. A diagnosis of achlorhydria must not be made until this form of stimulation has been tried. In fact, in adult gastro-enterology, the principal use of the histamine test at present is to differentiate between false and genuine achlorhydria.[14 15]

Histamine attracts attention because it stimulates and permits measurement of pure secretions instead of the mixture of juice, food, saliva and perhaps regurgitated intestinal juices which occupies the stomach following a test meal. Unfortunately, histamine, which is injected instead of administered by mouth, gives rise to an excessive secretory effect in place of the more normal mucosal response which follows the natural

taking of food. From the evidence one must conclude that for children as with adults the acidity values obtained with histamine have no clinical significance apart from uncovering true instances of achlorhydria.

Normal Values Following Ewald-type Meal. For adults the well-known Mayo Clinic[141] standards for normal men, based upon a test meal of arrowroot cookies and water, group themselves about a modal range of 45 to 50 for free acid, and 63 to 66 for total acid with most workers. Histamine stimulation gives figures 10 to 30% higher, on the average, than with the Ewald meal; the free hydrochloric acid occasionally rises to 150 or even more.

TABLE 1.—VALUES FOR FREE ACID IN NORMAL CHILDREN FOLLOWING
EWALD-TYPE MEAL

(Collected by Vanzant, Alvarez, Berkson and Eusterman[142])

Age (yrs.)	Males		Females	
	Mean	Standard deviation	Mean	Standard deviation
2	12 0*	8.0	9.0*	8.8
3	17.0	8.5	13.0	9.2
4	20.5	9.0	16 0	9.6
5	23.0	9.6	18 5	10 0
6	24.5	10.2	20.5	10 5
7	26.0	10.8	21.8	11.0
8	26.5	11.3	23.0	11.4
9	27.0	11.7	23.5	11 8
10	27.5	12.0	24.0	12 2
11	27.5	12.5	24.3	12 5
12	28.0	13.0	24.5	12.9
13	30.0	13.5	24.8	13 4
14	33.0	14.0	25.0	13.7
15	37.0	14.5	26.0	14 0

* Expressed as cc. N/10 HCl per 100 cc. gastric contents, or millinormal strength.

A good picture of the range of free acid in normal children after a simple Ewald-type test meal is given in the paper of Vanzant, Alvarez, Berkson and Eusterman.[142] Their figures were obtained by pooling the data of Jacobsen,[74] Klementsson,[76] Muhl,[105] and Wright[149] together with material from their department at the Mayo Clinic (Table 1). Increase with growth is clearly shown, as is also the tendency for boys to possess somewhat higher values than girls of the same age—a sex distinction which persists throughout life. One notes that the rate of rise is greater in the first few years than later on. Of striking importance is the magnitude of the standard deviation. The range represented by the standard deviation will include when added and subtracted from the mean slightly more than two-thirds of all the cases. Thus, for instance, at age 2 about two-thirds of the boys will exhibit free acid figures between 4 and 20.

It should be emphasized that this tabulation was compiled from a large group of single tests following a moderately stimulating carbohydrate meal. Other subjects of comparable age and health, or the same subjects if tested again at a later date, might have yielded statistics differing somewhat from these. In fact the data on normals from still other sources, such as Ogilvie's[108a] 60 children who had had porridge as a test meal, ran about 25% higher than the figures above given.

The figures of Vanzant *et al.* for age 1 year have been omitted from the reproduced table. There is a question how the test meals given to the younger infants in the first few months—whatever they may have been—compare in stimulant effect with the Ewald type used with the youngster beyond infancy. Again, as reference to the original sources shows, not all

the infants included in the tabulation were healthy and free from disease. Furthermore, the collecting into one single group of all infants 12 months and under masks completely the progressive increase in values which is taking place during this important year of rapid growth.

Newborn Period. Unexpectedly high acid values are found in the immediate postnatal period. This was first pointed out by Alfred Hess[?] in 1913, who aspirated the gastric contents of 55 unfed newborns under 15 hours of age. The quantity of juice obtained from each ranged from 0.3 to 5 cc., though 1 infant held 10 cc. and another 12 cc. of secretion. The possibility of this fluid consisting in part of swallowed amniotic fluid seems excluded by the further observation that on repeated aspirations free acid could be secured each time, indicative of its continual secretion. In one striking case a total of 17 cc. of highly acid gastric juice (free HCl 30 to 66) was secured within a 110-minute period. Pollitzer[117] made similar observations in a series of 100 unfed newborns. Griswold and Shohl's studies[49] on the fasting secretion in 25 normal newborns showed a pH range from 1.7 to 4.4 (numerical average 2.6).

Very recently Ritter[120] reported on the resting secretion in 36 unfed newborn infants $\frac{1}{2}$ to 14 hours after birth. In over 50% of the infants the free acid was higher than 20, reaching to 56 in 1 instance. Four showed no free acid. The pH ranged from 4.6 to 1.3. Attempted stimulation by milk and barley gruel provoked little response. Forty cc. of 2% Liebig's meat extract produced increase of total acid but none of free acid, presumably because of the buffer action of the contained proteins.

Cutter[25] is the only one to report on histamine stimulation of newborns. His series is too small to establish any generalizations; but 6 of 9 newborns 10 days old and younger produced free acid with histamine, the highest value being 20.

Miller[103] systematically followed the fasting acid with 50 normal infants from the 1st day of life until 1 month of age. Nearly all were breast fed. Specimens were taken 7 hours following the preceding feeding. The gastric acidity had its highest value on the 1st or 2d day of life, and then abated until the 7th day, after which it remained at a negligibly low level. Miller's data were summarized in the following table of averages:

Day	No. of cases tested	Free acid (Topfer's reagent)	Total acid (phenolphthalein)
1	45	17.2	38.0
2	40	15.4	37.9
3	41	4.5	24.6
4	40	1.0	21.7
5	40	0.7	22.3
6	40	0.2	17.6
7	40	0.4	11.2
8	41	0.0	11.2
9	40	0.0	11.3
10	40	0.0	11.7
11-15	41	0.7	12.5
16-20	50	1.0	16.9
21-30	45	2.1	18.0

The resting volumes recovered on aspiration were 1 to 3 cc. in the initial 2 days of life whereas after the 1st week when the acidity was feeble the volume decreased to 0.5 cc. or less.

Both Miller and Ritter suggested that the high values found in the immediately pre-natal period may be caused by some gastric secretory substance transmitted from the mother's blood stream. In evidence of

this hypothesis one may comment that none of the known hormonal secretion-stimulating substances, such as enterogastrone, exert their influence for more than a few hours following a single administration, and certainly not for a protracted period continuing as long as a week. A likelier cause for the phenomenon may lie in the erythrocyte disintegration and other proteinoclastic changes which take place during the first days after birth, while the newborn adjusts to the external environment and subsists on tissue reserves instead of external nourishment. Such catabolic processes are known to engender histamine-like products. Consequently the higher level of gastric acid secretory activity during the neonatal adjustment period may be construed as evidence for presence in the circulation of excessive amounts of these or related physiologic stimulants.

The Pavlov theory of acid secretion, described earlier, holds that the parietal secretion is an isotonic or nearly isotonic solution of HCl (concentration around 167 mN). None of the modern proponents[30c,48,65c] have published any special commentary with regard to the low content of free acid found in childhood, especially in the first year of life. If the theory is correct, the following peculiar circumstances must be active in all children: (a) the relative proportion of functionally mature parietal cells is much lower than in the adult stomach; or (b) the cells are not diminished in relative quantity but their *rate* of secretion is very slow, because of specific inhibition or lack of stimulation, with neutralizing secretions being formed with normal rapidity; or (c) the acid is being secreted at a normal rate from a full complement of cells but neutralizing mechanisms are operative to excess.

Inhibiting Effect of Fever. Yllpö[151] placed healthy infants in hot baths, which raised the body temperature to 38.5° to 40° C., and noted that the readings for hydrogen ion concentrations of their gastric juice were invariably about 1 point higher on the pH scale than before the induction of the artificial fever. A similar lessening of acidity was observed also in several vaccinated children. Daily reading of the fasting gastric contents showed a rise in the pH curves (denoting weaker acidity) reflecting almost exactly the body temperature curves. Marriott and Davison[95] found a slight reduction in intragastric hydrogen ion concentration in febrile infants ill with acute or chronic infections and Davison[32a] noted the same phenomenon in diarrhea cases. In both studies test meals of milk were employed. Bloomfield and Polland[14] describe a marked depression of gastric secretion amounting to transient complete anacidity in normal adults under artificial fever experimentally produced. The physiologic process which slows secretion of acid when body temperature is elevated has never been explained.

True Anacidity. True or complete anacidity is considered present only when no free acid is secreted following histamine stimulation. Among adults true anacidity is a chronic permanent condition. It is an almost invariable companion of pernicious anemia and occurs with great frequency in cancer of the stomach. There is a question as to how important a rôle true anacidity plays in the pathogenesis of the hypochromic microcytic anemia of middle-aged women, with which disorder it is very frequently associated. It is occasionally discovered as a random, unrelated finding in a great variety of disease conditions and occurs in many otherwise normal individuals. Distribution may be familial. Many subjects have remained entirely well over years of observation, never exhibiting evidence of gastric discomfort or disease.

Bloomfield and Polland[14] who made an exhaustive study of true anacidity

concluded that no case should be so diagnosed until certain rigid criteria had been complied with. Complete absence of free acid must be demonstrable by repeated analyses over an appreciable interval of time; temporary inhibitory influences such as fever, anxiety states and chronic infections must be excluded; histamine must not provoke secretion of hydrochloric acid, or perhaps but a trace. In most cases the gastric secretions will be found scanty in volume, rarely over 10 cc. in 10 minutes, with pH between 3 and 6, and total titrable acidity rarely exceeding 10. Only when tests for pepsin indicate that the quantity of this secretory element also has been reduced to a minimum may the designation of *achylia gastrica* legitimately be applied. With most clinically discovered cases of anacidity the histamine test, repeated if necessary, will usually bring out that the absence of acid is but false or transient.

When gastric analyses are performed on any large series of apparently normal adults, following fasting conditions, routine test meals or histamine, every possible degree of secretory activity, from none at all up to maximum rates, will be discovered. This point needs emphasis, since all evidence shows that the same sort of normal variation holds during infancy and childhood.

Instances of true histamine-resistant anacidity in childhood are rare. Insistence on refractoriness to histamine as a cardinal requirement for diagnosis excludes the data in all papers prepared prior to the introduction of the histamine test some 20 years ago,[22] as well as in many more recent publications. Indeed the number of children reported as being studied with histamine is astonishingly small in view of the great body of work which has been done on adults with this method. Dietrich and Shelby[23] studied 14 children aged 4 to 14 years and found free acid (from 19 to 117) in every case. Siemsen[123] reported on 40 tests with subjects 4½ to 13 years of age and demonstrated strong acid responses in all but 1. This exception was a 10 year old girl, weighing 25 kg., who following the injection secreted 15 to 28 cc. every 15 minutes with 0 free HCl and 4 to 6 total acidity. The diagnosis of "undernutrition" was recorded, and the statement that the mother had pernicious anemia. No repeat tests were done, and no other comments made. Neale's[106] data is sketchy and incomplete, but he appears to have investigated 29 children ranging from 6 months to 12 years of age without encountering anacidity. Faber *et al.*[37] found no cases in 7 normal young children, 3 under 1 year of age. In Ogilvie's[111] 99 rheumatic fever children tested after porridge only 1 consistently had no acid. "The boy with rheumatism appeared to have a persistent achylia; in 6 test meals over a period of 6 months no free acid was found and the total acidity, the chlorine and the peptic activity were low even with histamine. Ventriculin and large doses of iron improved his mild anemia and general condition without having any effect on gastric secretion." Not one of 60 other healthy children between 6 months and 12 years of age tested by Ogilvie had true anacidity. Lehmann is quoted by Miller[17] as having encountered one 12 month old infant with anacidity, but the published summary[91] fails to include any reference to this case. Cutter[31] tested 72 convalescent children (36 boys and 36 girls) between the ages of 4 days and 4 years on a hospital ward, excluding any recoveries from gastro-intestinal upsets and anemias. The only subjects having low values in the anacidity range were in the neonatal period: 2 prematures aged 17 and 20 days respectively, and 5 other infants aged 20 to 28 days. Repeat tests were not made. Miller[79] had failed to find free hydrochloric acid in the fasting contents of 6 out of 50 normal newborns who were

examined daily for the first 10 days of life. Two years later[103b] 1 of these 6 babies was retested, using histamine. No free acid was produced after sufficient histamine to cause cutaneous hyperemia of head and neck. The baby's birth weight and physical development had been normal, and to all appearances he was "a strong, healthy child."

True anacidity may be adjudged, therefore, as an exceptional circumstance during childhood. Affected children have not been followed long enough to answer the question as to whether the absence of secretion will always persist as happens with mature individuals, or whether it will eventually fade away and disappear. A further problem demanding elucidation deals with the ultimate fate of these children. Are they more likely to come down with pernicious anemia or other forms of anemia than are youngsters with unimpaired gastric acid secretion?

False Anacidity. The term "false anacidity" is applied to those cases in which secretion of acid follows histamine injection, but is otherwise not demonstrable under fasting basal conditions (known also as basal anacidity) or after a test meal (relative anacidity). False anacidity happens more often than does the true or complete variety. Miller[103b] surveyed much of the published data on normal children, and noted the condition to be recorded in 100% of infants aged 2 weeks, 35% aged 4 weeks, and about 17% for ages 3, 6 and 12 months. From the first year until adolescence with the Ewald meal, there was a gradual decrease in frequency. With adults, false anacidity is often associated with gastritis. In childhood the occasional absence of free acid except on strong stimulation cannot be so readily accounted for.

Hypoacidity and Hypochromic Anemia. The close and fundamental relationship between pernicious anemia and anacidity in adults has been known for years. Pernicious anemia, of course, is encountered almost never in childhood. Another variety of adult anemia associated frequently with either hypochlorhydria or true anacidity is microcytic hypochromic iron deficiency anemia, occurring chiefly among middle-aged women. Internists suspect that some sort of unidentified gastric malfunction exists in most of these cases.[16] It is improbable that the defect lies primarily in hydrochloric acid secretion, since oral administration of this acid in abundance will not correct the anemia,[16] but rather that, as in pernicious anemia, the acid secretory defect runs parallel with the lack in some "intrinsic factor" or anti-anemic principle.

That children having the familiar nutritional iron deficiency anemia often suffer from anacidity as well has been noted by Hawksley, Lightwood and Bailey,[57] Ogilvie,[108] Faber *et al.*,[37] Paxton,[113] Stewart,[124] and Wilson.[147] With most of their patients simple test meals, but not histamine, were used for the estimation of gastric acid secretory function.

Faber[37] studied 10 children between 7 months and 2 years of age having hypochromic iron deficiency anemia and defective acid secretion. With histamine, free acid was absent in 6 and low in the remaining 4 instances; total acidity and minute-volume were low in all. Every one made a speedy recovery with iron therapy. Four of the children were soon re-examined, and still had absence of free HCl, or mere traces. Two others, twins, were only 8 months old when first seen with anacidity and anemia. Seven years later 1 had still nearly complete anacidity and a mild anemia. The other was able to produce free HCl up to 50 following histamine, and had microcytosis but no hypochromia. Faber pointed out that the average healthy child in the first few years has a mild hypochromic anemia as compared with later childhood and adult life. He suggested that the

small quantity of gastric juice with its low content of acid which is secreted normally in early childhood may handicap iron absorption and contribute to the susceptibility to nutritional anemia at this age.

Stewart[134] compared the acidity responses to the alcohol test meal among several small groups of infants. Ten anemic infants exhibited some lowering of free and total acid as compared with a control group of 7 normals, but 7 other infants having other illnesses showed a more conspicuous diminution. Three infants when tested within 4 months after recovery from anemia had low or absent free acid, but a larger series of 12 infants and young children who had been ill with anemia 7 months to 3 years earlier all showed excellent acid production. From her limited personal observations and a perusal of the papers on record, Stewart was inclined to believe that there was no evidence for the existence of a congenital failure of gastric secretion as one basis for nutritional iron deficiency anemia in infancy.

Wilson[147] reported on 12 children with nutritional anemia, 10 under 5 years of age. Six of these when tested with alcohol and histamine produced no free gastric acid; 3 others produced no acid with alcohol alone (histamine not used), and 3 had low acid with histamine. Hydrochloric acid taken by mouth for an average of 11 days while receiving a simple ward diet failed to promote significant hemoglobin rise in any patient. An ensuing course of ferrous sulfate then produced excellent blood regeneration. Gastric analyses were unfortunately not repeated after recovery. Dacie and Ellman[29] have described an 8 year old girl with good preceding dietary history whose hypochromic anemia responded quickly to iron therapy. This case is interesting because histamine-resistant achlorhydria was found to exist both before and soon after recovery; later analyses were not made.

Related mechanisms may be at work in both the nutritional anemia of childhood and the microcytic hypochromic anemia of middle-aged women, but too little is known concerning the etiology of either for clear-cut declarations to be made. The conditions differ in that true anacidity is fairly common among the adults and persists after recovery from the anemia, whereas in childhood the available facts indicate that acid secretion returns with or soon after recovery. This is illustrated by one of Ogilvie's[173] cases. A child with simple iron deficiency anemia had no free hydrochloric acid even with histamine, but 1 month later, after improvement with iron medication a simple gruel test meal elicited the production of 13 free acid

worth.[24,40,89,104]   For example, out of Clyne and Rabinowitch's[24] 3 cases of duodenal ulceration, 1, a 13 year old girl following an Ewald test meal, had a maximum of 65 units total acidity and 45 units free acidity in $1\frac{1}{4}$ hours; another, a 7 year old boy, reached maximum levels of 35 and 20 respectively in $1\frac{1}{4}$ hours; and another 7 year old boy had peak rises to but 23 and 11 at 1 hour.   Not enough diagnostic examinations of the gastric contents in gastric or duodenal ulcer are on record to furnish adequate factual basis for clinical generalization.

Free Acid in Other Disease States.   With test meals average values for acid have been reported low in such conditions as asthma,[19] rheumatic fever,[108a] celiac disease,[57,108b] and anemia,[108] but the variability of individual cases has been so marked, and the number of cases so relatively small, that the statistical reliability of this supposed decrease may be gravely questioned.   No decrease occurs in infantile eczema.[28,103b]   In pyloric stenosis, according to Miller[103b] and Salmi,[123] gastric secretion prior to the onset of symptoms is normal in quantity and acidity.   As soon as vomiting begins, gastric stasis occurs with raised free and total acidity. Later hypochlorhydria develops, though the combined acid remains persistently elevated.   Steimann[133] reported on 58 children of all ages ill with a variety of diseases, measuring successive samples withdrawn through a small tube left *in situ* until the stomach had emptied.   Caffeine was employed as the stimulant.   Only 4 of these produced no free acid, 3 being refractory also to histamine, with recovery from their illness all but 1 began to secrete acid.   Pepsin was demonstrable in 3 of the 4 at the time of transient anacidity.   One only, a 10 year old girl complaining of abdominal pain, remained pepsin- and acid-free in spite of histamine stimulation.   During a period of hospitalization, she exhibited no anemia or other disturbances.   There is no note as to later reëxamination.   Apart from anemia as discussed above, there are no known disorders of childhood in which either anacidity, hypoacidity or hyperacidity occur regularly and consistently enough to be of service as diagnostic aids.

Summary and Conclusions.   Human gastric juice appears to contain no true rennin, its milk-clotting power being due to the pepsin content. Pepsin is present in indeterminate amount; it is questionable whether the pH drops low enough during infancy for its proteolytic action to be effective.   Attention is directed to a newly discovered digestive enzyme, cathepsin, which appears to be of importance in protein digestion, during early childhood especially, and to the minor ferments lipase, lipokinase, gelatinase, Brücke-pepsin and the amylase-activating factor.   The secretion of hydrochloric acid is low in infancy and increases with growth. In the immediately neonatal period acid secretion is temporarily increased. The fasting gastric secretion is an undependable index of acid secretory power.   Carbohydrate meals of the Ewald type are moderate stimuli, alcohol somewhat stronger, while histamine provokes an excessive and unphysiologic response.   Few cases are in record in which children with apparent anacidity failed to produce free acid on repeated tests with histamine.   Many children with anemia have transient anacidity unless stimulated by histamine, but the deficiency tends to clear as the anemia is corrected.   However there may be rare instances of anemia with complete or true anacidity in which acid is consistently absent.   With healthy children the range of values for acid production is so broad, regardless of the stimulus used, that the results of gastric analyses in disease conditions are almost always worthless.

REFERENCES

(1.) Aaron, A. H., Bockus, H. L., and Ivy, A. C.: Am. J. Digest. Dis. and Nutr., 1, 462, 1934. (2.) Ågren, G., and Hammarsten, E.: Enzymologia, 4, 49, 1937. (3.) Andersen, B.: Biochem. Ztschr., 262, 99, 1933. (4.) Andersen, B.: Investigations of Gastric Secretions of Infants, Levin & Munksgaard, Copenhagen, 1935. (5.) Anson, M. L., and Mirsky, A. E.: (a) J. Gen. Physiol., 16, 59, 1932; (b) Ibid., 22, 79, 1938.

(6.) Babbott, F. L., Johnston, J. A., Haskins, C. H., and Shohl, A. T.: Am. J. Dis. Child., 26, 475, 1923. (7.) Banu, Negresco, and Heresco: Compt. rend. Soc. de biol., 90, 1159, 1924. (8.) Barowsky, H., Tauber, H., and Kleiner, I. S.: Am. J. Digest. Dis. and Nutr., 4, 229, 1937. (9.) Beazell, J. M., Schmidt, C. R., Ivy, I. C., and Monaghan, J. F.: Am. J. Digest. Dis. and Nutr., 5, 661, 1938-39. (10.) Behrendt, H.: Jahrb. f. Kinderheilk., 102, 291, 1923. (11.) Bird, C. E., Limper, M. A., and Mayer, J. M.: Ann. Surg., 114, 526, 1941. (12.) Blakely, A. P. L., and Wilkinson, J. F.: Brit. J. Exp. Path., 14, 349, 1933. (13.) Bloomfield, A. L., and Polland, W. S.: J. Am. Med. Assn., 92, 1508, 1929. (14.) Bloomfield, A. L., and Polland, W. S.: Gastric Anacidity: Its Relations to Disease, Macmillan, New York, 1933. (15.) Bockus, H., Bank, J., and Willard, J. H.: Am. J. Med. Sci., 184, 185, 1932. (16.) Bockus, H.: Gastro-enterology, Saunders, Phila., Vol. I, 1943. (17.) Bowie, D. J., and Vineberg, A. M.: Quart J. Exp. Physiol., 25, 247, 1935. (18.) Bradley, H. C.: (a) Yale J. Biol. and Med., 4, 399, 1932. (b) Physiol. Rev., 18, 173, 1938. (19.) Bray, G. W.: Quart. J. Med., 24, 181, 1931 (20.) Buchs, S.: Ann. Paediat., 156, 1, 1940-41. (21.) Budde, O.: Ztschr. f. Kinderheilk., 47, 486, 1929.

(22.) Carnot, P., Koskowski, W., and Libert, E.: Compt. rend. Soc. de biol., 86, 575, 1922. (23.) Chievitz, I.: Acta paediat., 1, 416, 1921. (24.) Clyne, D. G. W., and Rabinowitch, J.: Arch. Dis. Child., 17, 102, 1942. (25.) Coari, A.: Pediatria, 35, 365, 1927. (26.) Copeman, W. S. C., and Hill, N. G.: Quart. J. Med., 22, 33, 1928. (27.) Council on Foods of the American Medical Association: Accepted Foods and Their Nutritional Significance, Am. Med. Assn., Chicago, 1939. (28.) Cutter, R. S.: J. Pediat., 12, 1, 1938.

(29.) Dacie, J. V., and Ellman, P.: Brit. J. Child. Dis., 39, 97, 1942. (30.) Davenport, H. W.: (a) Am. J. Physiol., 128, 725, 1940; (b) Ibid., 129, 505, 1940; (c) Gastroenterology, 1, 383, 1943. (31.) Davidsohn, H.: (a) Biochem. Ztschr., 49, 249, 1913; (b) Arch. f. Kinderheilk., 69, 142, 239, 1921. (32.) Davison, W. C.: (a) Am. J. Dis. Child., 30, 23, 1925; (b) Ibid., 63, 728, 1942. (33.) Dawson, A. B., and Ivy, A. C.: Am. J. Physiol., 76, 158, 1926. (34.) Demuth, F.: Ztschr. f. Kinderheilk., 35, 176, 1923. (35.) Dietrich, H., and Shelby, D. C.: Am. J. Dis. Child., 41, 1086, 1931. (36.) Dotti, L. B., and Kleiner, I. S.: Am. J. Physiol., 138, 557, 1943.

(37.) Faber, H. K., Mermod, C., Gleason, A. L., and Watkins, R. P.: J. Pediat., 7, 435, 1935. (38.) Fenger, F. J.: Am. Chem. Soc., 45, 249, 1923. (39.) Folin, O., and Ciocalteau, V.: J. Biol. Chem., 73, 627, 1927. (40.) Foxhee, J. C.: J. Am. Med. Assn., 99, 1336, 1932. (41.) Freudenberg, E.: (a) Ztschr. f. Kinderheilk., 46, 164, 1928 (b) Enzymologia, 8, 385, 1940 (Cathepsin); (c) Ann. paediat., 155, 121, 1940 II (Cathepsin). (42.) Freudenberg, E.: Physiologie und Pathologie der Verdauung im Säuglingsalter, Springer, Berlin, 1929. (43.) Freudenberg, E., and Buchs, S.: Schweiz. med. Wchnschr., 70, 249, 1940. (44.) Fruton, J. S., and Bergmann, M.: J. Biol. Chem., 127, 627, 1939. (45.) Fruton, J. S., Irving, G. W., Jr., and Bergmann, M.: J. Biol. Chem., 141, 763, 1941.

(46.) Gilman, A., and Cowgill, G. R.: J. Biol. Chem., 83, 743, 1929 (47.) Gompertz, L. M., and Cohen, W.: Am. J. Med. Sci., 177, 39, 1929 (48.) Gray, J. S.: Gastroenterology, 1, 390, 1943. (49.) Griswold, C., and Shohl, A. T.: Am. J. Dis. Child., 39, 541, 1925. (49.) Gianni, G.: Riv. di clin. pediat., 22, 656, 1941.

(50.) Hahn, M.: Am. J. Dis. Child., 7, 205, 1914. (51.) Hammarsten, O.: Upsala läkaref. Förh., 8, 63, 1872. (52.) Hammarsten, O.: (a) Ztschr. f. physiol. Chem., 67, 18, 1910 (b) Hoppe-Seyler's Ztschr., 121, 201, 1922. (53.) Hanke, M., Johannesen, R. E., and Hanke, M. M.: Proc. Soc. Exp. Biol. and Med., 33, 640, 1935 (54.) Hankinson, C. L., and Palmer, L. S.: J. Dairy Sci., 25, 277, 1942. (55.) Hankinson, C. L.: J. Dairy Sci., 25, 33, 1942. (56.) Harmele, M.: Recherches Chimiques Gastriques Chez le Nourrisson, Thèse de Paris, 1925. (57.) Hawksley, J. C., Lightwood, R., and Bailey, U. M.: Arch. Dis. Child., 9, 47, 1934. (58.) Helmer, O. M., and Fouts, P. J.: Am. J. Clin. Path. (Tech. Suppl.), 2, 11, 1938. (59.) Helmer, O. M., Fouts, P. J., and Zerfas, L. G.: J. Clin. Invest., 11, 1129, 1932. (60.) Helmer, O. M., Fouts, P. J., and Zerfas, L. G.: Am. J. Digest. Dis., 1, 12, 1934. (61.) Herriott, R. M.: J. Gen. Physiol., 21, 501, 1938. (62.) Hess, A. F.: Am. J. Dis. Child., 6, 264, 1913. (63.) Hess, R.: Jahrb. f. Kinderheilk., 81, 1, 1915. (64.) Hoerr, N. L., and Bensley, R. R.: Anat. Rec., 62, 117, 1935. (65.) Hollander, F.: Am. J. Dig. Dis., 194, 33, 1943.

(b) Am. J. Digest. Dis., 5, 364, 1938; (c) Gastroenterology, 1, 401, 1943. (66.) Hollander, F., and Cowgill, G. R.: J. Biol. Chem., 91, 151, 1931. (67.) Hollander, F., and Penner, A.: Am. J. Digest. Dis., 5, 739, 786, 1939; 6, 22, 1939. (68.) Holter, H., and Andersen, B.: Biochem. Ztschr., 269, 285, 1934. (69.) Holter, H., and Andersen, B.: Compt. rend. trav. lab., Carlsberg, vol. 20, No. 6, 1934–35. (70.) Holter, H., and Linderstroem-Lang, K.: Ztschr. f. physiol. Chem., 266, 149, 1934. (71.) Hurwitz: Thesis I.-D. Rostock 1920 (quoted by Bruning, H.), Deutsch. med. Wchnschr., 46, 883, 1920.

(72.) Ihre, B. J. E.: Human Gastric Secretion, Oxford Univ. Press, London, 1939. (73.) Inichoff, G. S.: Biochem. Ztschr., 131, 97, 1922.

(74.) Jacobsen, A. T. B.: Acta med. Scandinav., 52, 773, 1920.

(75.) Katsch, G., Baltzer, F., and Brinck, J.: Arch. Verdauungskr., 56, 1, 1934. (76.) Klementsson, E.: Acta pædiat., 3, 136, 1923. (77.) Klumpp, T. G., and Bowie, M. A.: J. Clin. Invest., 12, 1, 1933. (78.) Klumpp, T. G., and Neale, A. U.: Am. J. Dis. Child., 40, 1215, 1930. (79) Kraemer, M., and Townsend, L.: Am. J. Digest. Dis., 9, 338, 1942. (80.) Kraut, H., and Tria, E.: Biochem. Ztschr., 290, 275, 1937. (81.) Kronenberg, R.: Jahrb. f. Kinderheilk., 82, 401, 1915. (82.) Kunitz, M.: J. Gen. Physiol., 18, 459, 1935.

(83.) Langley, J. M.: J. Physiol., 3, 246, 1882. (84.) Lehmann, H.: Ber. u. d. ges. Physiol. u. exp. Pharmak., Abt. B., 87, 347, 1935. (85.) Leopold: Berl. klin. Wchnschr., 24, 734, 1887. (86.) Lichtenberg, H. H.: Ztschr. f. Kinderheilk., 54, 732, 1933. (87.) Lim, R. K. S.: Quart. J. Micr. Sci., 66, 187, 1922. (88.) Linderstroem-Lang, K.: (a) Ztschr. f. physiol. Chem., 176, 76, 1928; (b) Compt. rend. trav. lab. Carlsberg, vol. 17, No. 9, 1928. (89.) Logan, G. B., and Walters, W.: Ann. Surg., 113, 260, 1940. (90.) Luers, H., and Bader, J.: Biochem. Ztschr., 190, 122, 1927. (91.) Lundsteen, E.: Biochem. Ztschr., 271, 239, 1934. (92.) Lundsteen, E.: Biochem. Ztschr., 295, 191, 1938.

(93.) MacLean, H., Griffiths, W. J., and Hughes, T. A.: J. Physiol., 67, 409, 1929. (94.) Manchester, T. C.: Food Research, 7, 394, 1942. (95.) Marriott, W. M., and Davison, L. T.: Am. J. Dis. Child., 26, 542, 1923. (96.) Martin, L.: Am. J. Clin. Path. (Tech. Suppl.), 7, 50, 1937. (97.) Matthews, A. P.: Physiological Chemistry, Williams and Wilkins, Balt., 6th ed., pp. 605 ff., 1939. (97a.) Mathiesen, H.: Acta pædiat. 6, 145, 1926–27. (98.) Maximow, A. A., and Bloom, W.: Textbook of Histology, 4th ed., Saunders, Phila., p. 396, 1942. (99.) Meienberg, L. J., and Brown, C. L.: Ann. Int. Med., 7, 762, 1933. (100.) Mett, S. G.: Arch. f. Anat. u. Physiol. (Physiol. Abstr.), p. 58, 1894. (101.) Meyer, A.: Bibl. f. Læger., 8R, 390, 512, 1902. (102.) Michaelis: L.: Harvey Lectures, Williams & Wilkins, Balt., 22, 59, 1926–27. (103.) Miller, R. A., (a) Arch. Dis. Child., 16, 22, 1941; (b) Ibid., 17, 198, 1942. (104.) Moore, O. M.: Canad. Med. Assn. J., 44, 462, 1941. (105.) Muhl, G.: Acta pædiat., 3, 136, 1923.

(106.) Neale, A. V.: Arch. Dis. Child., 5, 137, 1930. (107.) Northrop, J. H.: (a) J. Gen. Physiol., 5, 263, 1922; (b) Ibid., 13, 739, 1930; (c) Ibid., 15, 29, 1931–32; (d) Ibid., 16, 41, 1932–33; (e) Harvey Lectures, Williams & Wilkins, Balt., 30, 229, 1934–35; (f) Crystalline Enzymes: The Chemistry of Pepsin, Trypsin, and Bacteriophage, Columbia Univ. Press, N. Y., 1939.

(108.) Ogilvie, J. W.: (a) Arch. Dis. Child., 9, 327, 1934; (b) Ibid., 10, 93, 1935; (c) Ibid., 10, 143, 1935. (109.) Osterberg, A. E., Vanzant, F. R., and Alvarez, W. C.: J. Clin. Invest., 12, 551, 1933. (110.) Oppenheimer, C.: Die Fermente und Ihre Wirkungen, Suppl., Dr. W. Junk, The Hague, 2, 863, 1939.

(111.) Parsons, L. G.: Lancet, 1, 797, 1924. (112.) Pavlov, I. P.: The Work of the Digestive Glands, G. Griffin, London, 1910. (113.) Paxton, W. T. W.: Glasgow Med. J., 7, 153, 1936. (114.) Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Williams & Wilkins, Balt., 2, 581, 1932. (115.) Polland, W. S.: J. Clin. Invest., 11, 449, 1932. (116.) Polland, W. S., and Bloomfield, A. L.: (a) J. Clin. Invest., 7, 45, 1929; (b) Ibid., 7, 57, 1929; (c) Ibid., 9, 107, 1930; (d) Ibid., 9, 651, 1931. (117.) Pollitzer, R.: La Pediatria, 29, 253, 1921. (118.) Portis, S. A.: Diseases of the Digestive System, Lea & Febiger, Phila., 1941.

(119.) Richardson, G. M.: Proc. Roy. Soc. London, B115, 121 and 142, 1934. (120.) Ritter, J. A.: Penna. Med. J., 44, 1321, 1941. (121.) Rosemann, R.: Handb. norm. path. Physiol., 3. S19, 1927. (121a.) Rosenbaum, S., and Spiegel, M.: Jahrb. f. Kinderheilk., 108, 87, 1925. (122.) Roughton, F. J.: Physiol. Rev., 15, 241, 1935.

(123.) Salmi, T.: Acta pædiat., 21, 362, 1937. (124.) Sauer, L. W., Minsk, L. D., and Alexander, W. G.: J. Am. Med. Assn., 79, 184, 1922. (125.) Schindler, R., Chamberlin, D. T., and Alvarez, W. C.: (Editorials) Gastroenterology, 1, 532, 1943. (126.) Seastone, C. V., and Herriott, R. M.: J. Gen. Physiol., 20, 797, 1937. (127.) Shohl A. T., and King, J. H.: Bull. Johns Hopkins Hosp., 31, 158, 1920. (128.) Siemsen, W. J., Am. J. Dis. Child., 44, 1013, 1932. (129.) Smith, E. R. B., and Cowgill, G. R.: Am. J. Physiol., 105, 697, 1933. (130.) Sörensen, S. P. L.: Biochem. Ztschr., 7, 45, 1908.

(131.) Spur, B., and Wolman, I. J.: Unpublished observations. (132.) Steinhardt, J.: J. Biol. Chem., 129, 135, 1939. (133.) Steimann, W.: Monatschr. f. Kinderheilk., 65, 264, 1936. (134.) Stewart, A.: Brit. J. Child. Dis., 34, 1, 1931. (134a.) Szydlowski, Z.: Jahrb. f. Kinderheilk., 34, 411, 1892.

(135.) Tauber, H.: Enzyme Chemistry, John Wiley, New York, 1937. (136.) Tauber, H., and Kleiner, I.: (a) J. Biol. Chem., 96, 745, 1932; (b) Ibid., 104, 259, 1934. (137.) Teorell, H.: J. Physiol., 97, 308, 1940. (138.) Tiselius, A., Henschen, G. E., and Svensson, H.: Biochem. J., 32, 1814, 1938. (139.) Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods, 9th ed., Saunders, Phila., 1912.

(140.) Van Slyke, D. D.: J. Biol. Chem., 83, 449, 1929. (141.) Vanzant, F. R., Alvarez, W. C., Eusterman, G. B., Dunn, H. L., and Berkson, J.: Arch. Int. Med., 49, 345, 1932. (142.) Vanzant, F. R., Alvarez, W. C., Berkson, J., and Eusterman, G.: Arch. Int. Med., 52, 616, 1933. (142a) vanDam, W.: Ztschr. Physiol. Chem., 61, 147, 1909.

(143.) Wilhelmj, C. M., and Sachs, A.: Am. J. Digest. Dis., 6, 467, 1939. (144.) Willheim, R.: Verhandl. d. Gesellsch. deutsch. Naturforsch. u. Artze (Vienna), 85 Versamml., 2 (teil 2), 1004, 1913. (145.) Wills, L., and Paterson, D.: Arch. Dis. Child., 1, 232, 1926. (146.) Willstätter, R., and Bamann, E.: Ztschr. f. physiol. Chem., 180, 127, 1929. (147.) Wilson, R.: Canad. Med. Assn. J., 41, 176, 1939. (148.) Wolman, I. J.: Unpublished observations. (149.) Wright, C. B.: Arch. Int. Med., 33, 435, 1924. (150) Wright, I. S., DeSanctis, A., and Killian, J. A.: Proc. Soc. Exp. Biol. and Med., 27, 782, 1930.

(151.) Yllpö, A.: Acta pædiat., 3, 213, 1924.

(152.) Zweifel, O.: Untersuch. ueber d. Verdanungsapparat. d. Neugeb., 1874 (quoted from Hess, Ref. 62).

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BENIGN LESIONS OF THE CERVIX

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factor in cancer. Opinion concerning their causal relation to cancer indicates that birth trauma is regarded as a much more important factor. The remainder of those replying indicated that non-specific infections rate second as precancerous lesions and specific infections third. Questions relative to the investigation of cervicitis revealed that the majority did not feel that smears were important and that biopsy was indicated in only a few cases. Most of the men were of the opinion that the Schiller test and colposcope added little to the investigation of this condition. It would seem, therefore, that, in general, gross inspection of the lesion was thought to be adequate to make the diagnosis and to decide on proper treatment. By far the most common form of treatment used is actual cautery. The next in order of frequency are the 3 operative procedures: Sturmdorf amputation, trachelorrhaphy, and conization, which occupy about comparable positions. Cautery with chemical agents occupied a position quite similar to these 3 procedures, and cautery under anesthesia is next in importance. The incidence of complications following treatment was surprisingly large. An analysis of the 3 chief complications, hemorrhage, stenosis and infection, revealed that cautery was responsible in 35%, 38%, and 54%, respectively. Since there has been considerable discussion concerning the relative merits of conization and Sturmdorf amputation, a comparison of complications following these was thought desirable. It was noted that the total number of complications was about the same. There is a higher incidence of hemorrhage and infection with conization, while the incidence of stenosis of the cervix following the Sturmdorf operation is sufficiently high almost to equalize this. In view of the large number of complications reported, it is of interest to study the opinion concerning contraindications to treatment. It was noted that retroversion which has been emphasized by many as a contraindication was regarded as insignificant by 80% of those replying. The fact, however, that 97% avoided treatment in active infection and yet 148 acute infections attributable to the treatment were reported, suggests that the method of diagnosis of infection of the upper genital tract or its activity may be lacking in efficiency.

Until comparatively recent times cervicitis was treated by a variety of douches and the application of medicines by means of tampons; but since the effect of such treatment was only upon the superficial cells, it has been largely replaced by various forms of cauterization. At the Mayo Clinic, according to Piper,[14] of 640 patients whose cervices had been cauterized and who replied to questionnaires 6 to 9 years after treatment, 1 patient only reported the development of cancer. That patient had had a polyp removed and its base seared by the cautery. She was treated elsewhere for epithelioma of the cervix 4 years later. That chronic cervicitis is a source of infection is demonstrated by the relief of chronic backache, and also by the improvement in the sensation of pelvic heaviness, in some malpositions of the uterus and in tenderness of the uterine ligaments after application of cautery to the cervix. In a series of cases from the Clinic of 358 patients who have had an associated lumbosacral type of backache 62.8% were relieved and 11.4% reported the backache improved.

The results of treatment of 611 patients at the Hospital of the University of Pennsylvania have been presented by Tompkins.[16] The methods of treatment were cauterization, trachelorrhaphy, Sturmdorf operation and amputation. Each method gave relief of leukorrhea in approximately 85% of cases. Trachelorrhaphy gave a lower percentage

of eradicating deep-seated chronic infections of the cervical canal in older women. (3) As a complete substitute for the Sturmdorf operation in any condition of the cervix for which the Sturmdorf operation is indicated. (4) As a means of obtaining adequate biopsy material in cases in which original biopsy material presented cytologic abnormalities strongly suggesting neoplastic change. (5) As a substitute for older methods of trachelorrhaphy in most women but especially in elderly women. Extensive conization as here described is a hospital procedure and should be reserved for the more severe types of cervical lesions. No serious immediate complication occurred in any of the conizations comprising this study. During the first few days there is little discomfort but commencing the 3d or 4th day the discharge becomes profuse and is often bloody. Normally this discharge persists for 2 weeks, after which it gradually decreases. Vaginal cleansing douches are essential during this healing period, the type of douche making but little difference. Ultimate healing with complete epithelization renders the cervix clean and normal in appearance. In a few patients small areas of delayed epithelization are noted. In these, healing may be hastened by the use of the fine nasal tip cautery. Strictures occurred in about 9% of the cases. The majority were mild and required only dilatation or passage of a sterile sound or hemostat. The fact, however, that strictures do occur, some of them severe, warrants care in the selection of cases and careful observation afterward. While the number of pregnancies subsequent to conization in this series is small, the trend certainly suggests a harmful influence on subsequent pregnancies. This is seen to be in the direction of abortion and premature labor rather than cervical dystocia as might have been anticipated. This tendency to early interruption of pregnancy is another drawback and suggests its use only in women past the childbearing period, and even then they do not consider it a substitute for the less radical office procedures in mild cervical disease.

A method of chemical cauterization using zinc chloride without the necessity of an anesthetic has been reported by Bourne, Bond and McGarrity.[2] Porous clay pencils were used as the medium for introduction. They were $1\frac{1}{2}$ inches long and of different diameters. If these pencils are placed in a saturated solution of zinc chloride for 10 minutes, they will become fully charged with the salt and ready for use. In most cases there is no difficulty in inserting one of a suitable size without pain, and it is easy to remove by the wire passed through a hole drilled in the proximal end of the pencil. The absorption of zinc chloride by the tissues is fairly constant according to the size of the pencil and the duration of the application and it is sufficient to produce necrosis of the mucosa extending from about 2 to 4 mm. deep. If the dose of zinc has been insufficient, either because too small a pencil has been used or because the time of application is too short, the zone of necrosis will be uneven or not deep enough to affect all the glands, and partial failure will follow; on the other hand, if the dose has been excessive, necrosis may penetrate too deeply. In these cases a large slough, representing a cast of the major part of the cervix, tunneled by its canal, may separate about the 7th day, but even though so much tissue has been removed they have never seen anything more than very slight bleeding at the time of separation. The type of cervix most suitable for treatment by zinc chloride is the one that has not been deeply lacerated and is therefore able to hold the pencil in close contact with its wall throughout its whole length. A strip of gauze moistened with a 5% solution of sodium bicarbonate is loosely packed around the

cervix and firmly against the os to maintain the pencil in position. The pencil is withdrawn in from 2 to 4 hours, depending on its size. No further treatment is necessary. The subsequent clinical course is as follows: For 2 or 3 days there is no discharge; this is due to the complete necrosis of the mucous membrane, which has not yet begun to separate as a slough. About the 3d or 4th day it reappears and increases until the 6th or 7th day when a little blood is usually noticed. This corresponds to the separation of the necrotic mucosa as a slough either in one well-defined gray mass or in the form of small particles and shreds. For a few days there is a profuse seropurulent discharge, which gradually diminishes during the next 4 weeks until finally there is nothing more than the normal moisture of the vagina.

The use of ionization in the treatment of chronic cervicitis has been very encouraging to Forman[4] who has treated 93 patients and given 389 treatments. Of these, 71 patients were discharged as completely cured. There were 6 complete failures; these patients had a pelvic inflammatory disease with a palpable mass confusing the picture. Seven patients after receiving the full course of 6 treatments were relieved of the profuse discharge, but, clinically, were not cured, a definite erosion with edema of the cervix being present.

Method. The technique employed is as follows: The ionization apparatus delivers a direct galvanic current which is controlled by a rheostat and measured by a milliampere meter gaged to 25 milliamperes. The instrument has two poles The negative one is attached to a specially designed indifferent electrode covered with a wet felt pad. To the positive pole is attached the intracervical copper electrode which is made in 5 sizes, designed to fit the cervical canal without entering the internal os. The wet felt pad connected to the negative pole is placed under the buttocks of the patient. A bivalve speculum is then introduced, the cervix exposed, and secretion removed. The proper sized copper electrode is inserted to the internal os. If the external os is too small to admit even the smallest electrode, the tip of the electrode is introduced and the negative current is turned on slowly. Five to 10 milliamperes used for about 5 minutes causes softening and relaxation of the tissues about the external os, permitting the further insertion of the instrument. After the electrode his been properly placed, the positive current is turned on, the rheostat is turned slowly until the milliameter registers from 8 to 20 amperes, depending upon the amount of current desired. The larger the area of the electrode in contact with the cervical canal, the greater the amount of current. After a minute or two, the electrode adheres to the cervical mucosa. Cotton is then packed against the cervix surrounding the electrode to prevent its displacement. At the end of 15 or 20 minutes, crystals of copper oxychloride may be seen to surround the electrode and external os. The current now is turned off slowly, the electrode withdrawn, and the cervical canal is seen to be covered by a layer of copper crystals. Very often, due to superficial electric coagulation and dehydration of the tissues of the cervix, the electrode becomes adherent to the cervical mucosa. This necessitates the use of the negative current for 2 or 3 minutes in order to allow the withdrawal of the electrode without undue trauma to the cervical mucosa. The patient is then instructed to take a cleansing douche every night and to return in 2 weeks for another treatment; 4 to 6 such treatments are usually sufficient in clearing up the average case of endocervicitis with erosion. Most patients have complained of some degree of cramplike pain in the lower abdomen during and for several hours after the treatment. In a few cases the pain was severe enough to confine them to bed for 1 day, but no other untoward effects were noted. In no case has there been any evidence of bleeding or slough. His experience with this method leads him to believe that it approximates, more closely than any other thus far advocated the ideal treatment for endocervicitis. The deposition of copper as copper oxychloride produces a marked bactericidal effect. The mild coagulating property of the positive current causes a shriveling and obliteration of the infected glands, while the technique of treatment keeps

the cervix well dilated, bring all the mucosa and the openings of the cervical glands in contact with the electrode and, what is more important, permitting adequate drainage.

Stricture. In one of his characteristically instructive papers Curtis[6] states that the frequency of cervical strictures merits repeated emphasis; they are of common occurrence in the practice of everyone concerned with pelvic diseases of women. The various therapeutic procedures employed in the treatment of lesions of the cervix are more important than any other factor in the etiology of cervical obstructions. Endocervicitis is also important in the etiology, and in the majority of cases of serious stricture there is a history of an inflammatory process as well as of instrumentation. It must not be assumed, however, that absence of a history of infection or of instrumentation invariably gives assurance of a patent cervical canal and adequate uterine drainage. Marked strictures are encountered in virgin patients and in others in whom there is no discoverable predisposing factor. Fibrotic constriction of the cervical lumen is much more serious than simple obstruction by adhesions. If drainage is not free, pocketing of the cervix may occur immediately above the fibrous obstruction. Metaplasia of the columnar epithelium into squamous epithelium has been found in the roughened pocketed endocervix above a cervical stricture. Irritation from retained secretions may be a factor in stimulating the metaplasia. Tumorous nodulations of the endocervix and lower uterine segment are a less common cause of uterine obstruction. The effects of damming back of uterine secretions and menstrual blood may be far reaching—perhaps important in the etiology of endometrial polyps, adenomyosis of the uterus, pelvic endometriosis, and back pressure inflammatory processes in the pelvis. The relationship of obstructive retention to the development of intra-uterine cancer is a problem which merits further study. He believes it will eventually be regarded as a surgical sin to use radium, or make repeated endocervical topical applications, or apply the cautery within the cervical canal, or amputate the cervix of the uterus, or even administer expectant care to a patient with notable endocervical disease, without prolonged and attentive observation thereafter directed to the maintenance or patency of the cervical canal. Our thoughts have been too little concerned with the lumen of the uterus and the importance of free uterine drainage.

Reviewing the ultimate results in a series of 261 patients operated upon at Woman's Hospital, New York, for chronic cervicitis, Bullard[3] finds that for the cure of cervical leukorrhea high amputation is perfect, Sturmdorf operation excellent, low amputation very good, and trachelorrhaphy disappointing. Varying degrees of cervical stenosis followed high amputation in 54% of the cases, low amputation in 18%, trachelorrhaphy in 12%, and Sturmdorf tracheloplasty in 1.8%. Of 59 cervices repaired by high amputation, 23 were impenetrable by a probe, yet only 2 had obstructive dysmenorrhea. Only 2 out of 59 operated upon required operative dilatation later. There was much less stenosis after low amputation (18%), only 2% had obstructive dysmenorrhea while there was no obstructive dysmenorrhea after trachelorrhaphy. The Sturmdorf operation gets a well-nigh perfect record of non-interference with subsequent pregnancies and labors. One case of serious cervical dystocia followed a unilateral trachelorrhaphy, and this type of operation may have caused a premature labor in another; but there were 9 entirely normal labors in patients who had a previous trachelorrhaphy. No dystocia and no abortions followed low amputations, and there were 8 normal labors; but this

operation was the cause of at least 1 premature labor and perhaps of 3 others. Of 4 pregnancies after high amputations 2 terminated in premature labor; and 2 aborted from undetermined causes, a bad record. Diathermy may replace surgery in the treatment of chronic cervicitis; but only if it will eradicate the entire diseased area as dependably as a knife and show a better record in subsequent labors than the Sturmdorf operation. The degree of scarring following diathermy has not been sufficiently demonstrated.

The Retained Cervix. For many years there has been discussion among gynecologists as to the advisability of removing the cervix in all cases where hysterectomy is performed. Those in favor of complete hysterectomy base their opinion on the danger of the development of carcinoma in the retained stump. A study which has been made by Henriksen[2] is of interest because while he shows that the incidence of cancer is low, there are other symptoms which develop in a small percentage of patients whose cervix is retained. The alteration in the vascularity of the retained cervices, together with the loss of the changes in diameter of the cervical canal which normally accompany menstruation, tend to stricture formation, with subsequent cervical pyometra. These strictures and abscesses are often overlooked in routine examination, especially when the portio vaginalis presents a grossly normal smooth surface and a small external os. Not infrequently it is this type of cervix that constitutes the causative source of backaches, urinary symptoms and a persistent leukorrheal discharge. Simple dilatation of the cervical canal usually results in quick relief. In a series of 6550 stumps, he has records of 157 patients returning because of complaints relative to the stump. Of the 157 patients, 26 were found to have primary carcinoma of the stump.

The common cause of periodic vaginal bleeding following sub-total hysterectomy is high amputation of the corpus, and the bleeding is therefore an indication of menstrual activity. Of 22 patients presenting irregular vaginal bleeding, 7 had definite malignancy of the stump. This is the most dangerous group in the series. Patients are frequently advised not to be alarmed if they experience scant bleeding on several occasions following sub-total hysterectomy. Naturally, the patient is likely to interpret such bleeding when it does occur as of no importance. Again, not infrequently abnormal bleeding may even appear several years following the operation and may then be considered as an indication of the menopause. The patients in this group in whom benign lesions were found, presented for the most part functioning endometrium in association with chronic infections of the cervix or cervical polyps and were treated by cervical cauterization. Of the 32 patients complaining of an inoffensive vaginal discharge, varying in amount from a self-termed "moderate" to "profuse," 3 had cancer of the stump. Six of the 19 patients presenting a foul discharge and no evidence of bleeding were found to have cancer. There were 20 patients complaining of vaginal discharge with various degrees of bleeding; 9 of these had cancer of the cervical stump. Many of these patients who complain of leukorrheal discharge in the absence of cancer show definite evidence of stricture about the external os, in spite of the presence of deep lacerations. He treats these strictures by dilating the canal to the size of a No. 12 Hegar dilator, generally this is more efficacious than the cautery, but care must be taken not to tear the cervix during the insertion of the dilators. The fact that only 2.4 % (157 patients) of the 6550 patients returned to the hospital with complications referable to the stump, and that of these he has records of only 26 or a percentage

of 0.45 showing cancer, indicates that the incidence of stump cancer is so low as to be of relatively little import. There is no evidence that subtotal hysterectomy predisposes to cancer of the stump or that the residual stump is more susceptible to malignant changes than the cervix of a complete uterus. He does not feel that the 0.45% incidence of stump cancer is sufficient reason to advise the total operation with its morbidity-mortality rate of 2 to 5%. It is common knowledge that in the hands of the less experienced surgeon, total hysterectomy is accompanied with greater risk than when the more conservative operation is employed. The more rational approach would be to fit the operation to the patient and to the physical findings, rather than to advocate either operation as a routine. With proper pre- and postoperative treatment of the cervix, total hysterectomy merely as a prophylactic against cancer of the stump is probably rarely indicated.

The development of a fibromyoma in the cervical stump following hysterectomy is very unusual. Based on an experience of 4 such cases Hyams[10] states that these tumors grow more rapidly than those of the body of the uterus and may attain a considerable size. The majority originate in the posterior portion of the cervical stump and tend to grow backwards toward the cul-de-sac. They may be retroperitoneal, intraligamentary, or subvesical. The first manifestations are usually obstructive, due to pressure of the growth, and consist of marked constipation, pain in the abdomen or pelvis, and if adhesions are present, drag on the adjacent viscera. With pressure on the bladder, the patient complains of urinary disturbance, urinary frequency, urgency, incontinence, or retention. Vaginal bleeding or discharge is frequently present; it may be slight or profuse. In 1 of his patients, the bleeding was so severe that immediate transfusion was necessary. If the possibility of such a tumor is borne in mind, the diagnosis should not be difficult. It is based on palpation of a solid tumor attached to the cervical stump. If the mass fills the pelvis, there may be some confusion as to the origin and type of tumor, particularly if the uterine adnexa have not been removed or dense adhesions are present. Because of the location of the growth and possible distortion of the ureters or bladder, a careful urographic study of the urinary tract should be made to determine the relation of these structures to the tumor before treatment is instituted. Surgical intervention should be prompt. Because of the site of the growth and its tendency to grow upward and backward, the abdominal route offers the best method of approach. The operation may be difficult and tax the skill of the surgeon, as dense adhesions usually present may cause malposition, distortion or fixation of the adjacent structures. Once free, the tumor is easily shelled out. The possibility of distortion of the bladder from a previous operation or possible atypical position of the ureters should not be overlooked, and care must be taken in the identification, separation, and preservation of these structures. If the tumor mass is found so adherent to the bladder that separation cannot be accomplished without injury to the viscus, it is advisable to resect that portion of the bladder with the tumor mass, and repair the opening in the bladder wall. There is usually considerable venous oozing from the cavity from which the tumor is enucleated and this is best controlled by packing. All raw areas should be peritonized.

Tuberculosis. While all investigators admit that tuberculosis of the cervix is a rare disease, it merits consideration because of its clinical resemblance to carcinoma. In a report based on 191 cases Collins[5] states that in approximately 85% of the cases it is secondary to a tuberculous

focus found in the lungs or in either the gastro-intestinal or the genito-urinary tract. Of the 185 cases which he has studied from the literature, in 156 (84.3%) there was demonstrable tuberculosis elsewhere. In 102 cases (55.1%) genito-urinary tuberculosis was present in either an active or a quiescent stage. Marriage and pregnancy are two common contributing etiologic factors. Tuberculosis of the female generative tract occurs most frequently in the Fallopian tubes and progressively diminishes in frequency as it approaches the uterine cervix. It is believed that this disease usually results from a descending infection spread by contiguity from foci situated higher in the pelvis or by hematogenous and lymphogenous routes from distant foci. Primary tuberculosis of the uterine cervix is rare. In this series of 185 cases studied from the literature there were 16 proved instances of this type of primary infection. A true example of primary tuberculosis of the uterine cervix must fulfil the criterion of being the only focus of tuberculosis in that patient. Tuberculosis of the cervix uteri is classified into 4 types: the ulcerative, the papillary, the miliary and the rare bacillary catarrhal. Thus the gross appearance of the cervical lesion may vary widely. The typical lesion is usually ulcerated. The edges are either well defined or undermined and are surrounded by either tubercles or normal-appearing tissues. The adjacent portions of the vagina may be involved, and tubercles may be seen. Secondary infections are commonly superimposed on these lesions. Varying degrees of bleeding or even severe hemorrhages with accompanying foul leukorrhea are frequently encountered. Microscopically, typical tubercle formation is commonly seen. Often atypical tubercles composed of only epithelioid and lymphocytic cells may be the only evidence on which a presumptive diagnosis of tuberculosis can be made. Acid-fast stains for the presence of the tubercle bacillus in either the microscopic section or the tissue smear may be apparently negative. Inoculation of guinea pigs may prove to be the only reliable method by which a correct diagnosis can be established. Biopsy is a quick correct method of establishing a probable diagnosis. Removal of such a specimen will not injure the patient, while the issues at stake are of such gravity as to make a correct diagnosis imperative. The treatment of tuberculosis of the uterine cervix should preferably be of radical surgical character, such as abdominal panhysterectomy with the possible preservation of one ovary, if the patient's condition and other factors are favorable, because usually extensive tuberculous disease of the upper pelvic part of the generative tract is present and must be eradicated if cure is to result. For that reason and because of the rarity of a primary tuberculous infection of the cervix, local treatment of the cervical lesion is not advisable. For similar considerations Roentgen and radium therapy will often prove to be disappointing in their end-results. The contraindications to the employment of surgery are advanced local tuberculous lesions with extensive involvement of the neighboring bladder or rectum, extensive tuberculous salpingitis, marked secondary infection, the presence of active tuberculous foci elsewhere, cardiovascular disease and senility.

At Peiping, Lin[12] found 21 cases of pelvic tuberculosis over a period of 15 years. He found that it occurs most frequently during a period of sexual activity and may be due to either exogenous or endogenous infection. It produces no pathognomonic symptoms although menstrual disorders, hemorrhage, leukorrhea and sterility are common complaints. The disease is frequently confused with cancer and the definite diagnosis can sometimes be made only by microscopic examination. The treatment

depends on whether the disease is primary or secondary in the cervix. If primary, radical surgery is indicated, but if secondary, often associated with tuberculosis in the lungs, tubes and ovaries, palliative local treatment is probably the wisest procedure.

Danforth[7] concurs with the preceding authors that in the great majority of cases it is secondary to tuberculosis at higher levels of the genital organs which in turn are usually preceded by lesions elsewhere, usually in the lungs, from which the tubercle bacilli find their way to the pelvis *via* the blood stream. Infections from external contact are rare. The symptoms are usually not marked and consist largely of leukorrhea. The disease is frequently mistaken for cancer although the typical induration of cancer is absent and the lesion does not bleed as easily on contact. He states that radiotherapy should not be used but the best treatment is complete hysterectomy if the condition of the patient permits. If it is quite certain that tuberculosis of the cervix is primary, amputation of the cervix will be a satisfactory operation.

Granuloma Venereum. Another benign lesion which may be confused with carcinoma is granuloma venereum, also known as granuloma inguinale. The recognition of this disease in the cervix is comparatively recent since Pund, Huie and Gotcher[15] were unable to find a single case of granuloma venereum of the cervix in the files prior to 1934. However, since 1934 9 cases were observed and this confirms the impression that venereal granuloma is on the increase. The 9 cases were found in the 830 biopsies of the cervix which were performed between Jan. 1, 1934, and March 31, 1938. This is 1.1% of all cervices that were biopsied. Of these 830 patients, 694 were white and in none was the diagnosis of granuloma venereum made. Of the biopsies from the 136 negro patients, 9 were positive for granuloma venereum, an incidence of 6.6%. If the 69 carcinomas are eliminated from this group, we find that 13.4% of the remaining 67 negro patients who complained of cervical lesions, suffered from granuloma venereum.

In an analysis of 38 cases of this disease Arnell and Potekin[1] state that it is now generally agreed that granuloma inguinale should be regarded as a venereal infection, even though extragenital lesions have been described. The Donovan body, which is the specific etiologic agent in granuloma inguinale, is a microörganism which probably belongs to the protozoan group, although there is some evidence to suggest that it may be a fungus. It is pathogenic only for man and is transmitted only by direct contact. It has never been cultured. The incubation period is thought to be 40 to 60 days. The lesion of granuloma inguinale of the cervix appears first as a soft, red, granular macule. It enlarges rapidly and sometimes ulcerates early, forming a shallow, granular ulcer with well-defined edges. Sometimes it develops as a hypertrophic granular mass in which are numerous small areas of ulceration. In advanced stages the entire cervix may be replaced by a large cauliflower mass of soft, friable bleeding tissue. The cervical lesion may extend to the adjacent vaginal walls and may completely fill the vaginal vault, or, occasionally, may be combined with only a few discrete vaginal lesions, or even a single lesion. Microscopic examination of the lesion reveals characteristic exuberant granulation tissue in which the pathognomonic cell is found. The essential feature of the histopathology is the presence of large monocytes with many intracytoplasmic spaces in which the Donovan bodies are dispersed. These bodies, which are elliptical or round and stain deeply, are usually arranged peripherally in the intracytoplasmic

spaces. Sometimes, however, they are scattered through the cell, or appear as one or more collections, pushing the nucleus to the side. Of the 38 patients, 34 were colored and only 4 white, these figures being in agreement with the high proportion of negroes with granuloma inguinale of the external genitalia reported in the literature. Apparently these are the first cases of cervical granuloma inguinale to be reported in white women. A purulent or bloody vaginal discharge, hemorrhage, and pelvic pain were the chief complaints for which the patients sought relief. The earliest symptom was usually a serous discharge, followed successively by purulent leukorrhea, blood-stained leukorrhea, or in some instances, by profuse vaginal hemorrhage. Bleeding was present in 31 of the 38 cases, the prominence of this symptom being due to the tendency of the lesion toward early ulceration, with involvement of the highly vascularized cervical tissue. Thirty patients complained of pain or discomfort in the lower abdomen, usually associated with backache. The pain was bilateral in all but 4 instances. Many patients exhibited parametrial and adnexal thickening and tenderness upon pelvic examination, and 8 had palpable masses in the pelvis. In many, if not in most cases the pelvic inflammatory disease was concomitant or preëxistent, and not the result of the cervical infection, for a large percentage of the colored women treated at Charity Hospital exhibit pelvic disease. In other instances the associated pelvic disease was apparently due to secondary infection of the primary cervical lesion, with lymphatic extension to the pelvis. Direct extension of the granuloma inguinale to the pelvis may also occur, with involvement of the uterus, tubes and ovaries. Ten of the 18 patients who were hospitalized had temperatures above 100° F., and 14 had sedimentation rates of less than 30 minutes. Many were anemic and complained of weakness, thus demonstrating the effects of blood loss and of chronic infectious processes. The duration of symptoms varied from 1 week to 3 years. Most of the long-standing cases represented untreated or chronic lesions, or perhaps recurrences, rather than reinfections. About one-half of the patients sought relief in less than a month after the onset of symptoms, apparently because of the foul-smelling, sanguinopurulent discharge which caused sufficient discomfort to force them to seek early medical consultation. The interval is unusually short for colored patients who tend to delay medical consultation whenever severe pain is not a prominent symptom. Antimony compounds are considered specific in granuloma inguinale and should be employed routinely, although, if special indications are present, it may be necessary to employ other measures also. They prefer tartar emetic to fuadin. It is given intravenously twice or 3 times a week, in doses of 10 cc. of 1% solution. Local therapy is also advised in all cases. They have had the best results with topical applications of neoarsphenamine (4.5%) in glycerin to combat fusospirochetosis and secondary infections and to promote healthy granulation tissue. They also employ potassium permanganate irrigations (1:1000 solution) to alleviate local irritation and to overcome the odor of the discharge. In most cases clinical improvement was noted within 3 to 4 weeks after treatment was begun. In 1 instance cure was effected by 4 injections of tartar emetic given over a 4 weeks period, but the average duration of treatment was 3 months. The longest course of treatment was 14 months. It is most important that treatment be continued long enough to effect a permanent cure; the tendency is to discontinue it when signs of superficial improvement are evident. Chronic lesions are often resistant to therapy, but early lesions usually respond rapidly, and prompt

diagnosis is therefore essential to a rapid cure.   Recurrences with any form of therapy are unfortunately common.   The therapy of granuloma inguinale of the cervix during pregnancy demands a special note since the response to tartar emetic therapy is poor.   Large growths may complicate labor and introduce serious hazards of hemorrhage and infection.   Delivery from below should always be employed if it seems safe.   If, however, the cervical growth is extensive or if concomitant lesions of the external genitalia have produced so much scar tissue that vaginal delivery seems unwise, Porro Cæsarean section may be necessary.

REFERENCES

(1.) Arnell, R. E., and Potekin, J. S.: Am. J. Obst. and Gynec., 39, 626, 1940.   (2.) Bourne, A., Bond, L. T., and McGarrity, K. A.: Brit. Med. J., 1, 116, 1937.   (3.) Bullard, E. A.: Am. J. Obst. and Gynec., 27, 668, 1934.   (4.) Cannell, D., and Douglass, M.: Ibid., 30, 376, 1935.   (5.) Collins, D. C.: J. Am. Med. Assn., 112, 605, 1939.   (6.) Curtis, A. H.: Surg., Gynec. and Obst., 60, 930, 1935.   (7.) Danforth, W. C.: Ann. Surg., 106, 407, 1937.   (8.) Forman, I.: Am. J. Obst. and Gynec., 32, 503, 1936.   (9.) Henriksen, E.: Ibid., 37, 452, 1939.   (10.) Hyams, M. N.: Ibid., 37, 690, 1939.   (11.) Kretzschmar, N. R., Randall, L. M., and Brewer, J.: Ibid., 39, 665, 1940.   (12.) Lin, S.: Chinese Med. J., 50, 1025, 1936.   (13.) Miller, N. F., and Todd, O. E.: Surg., Gynec. and Obst., 67, 265, 1938.   (14.) Piper, M. C.: Proc. Staff Meet. Mayo Clin., 11, 689, 1936.   (15.) Pund, E. R., Huie, G. B., and Gotcher, V. A.: Am. J. Obst. and Gynec., 37, 477, 1939.   (16.) Tompkins, P.: Ibid., 30, 369, 1935.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF OCTOBER 19, 1943

The Incidence of Hemolytic Anemia in Mice Fed Diets Containing Sulfamerazine, Sulfadiazine, or Sulfapyridine.   ALBERT R. LATVEN and ARNOLD D. WELCH (Department of Pharmacology, Medical Research Division, Sharp & Dohme, Inc., Glenolden, Pa.).   Hemolytic anemia is occasionally seen when sulfonamides are administered to man.   In the mouse, however, an anemic condition of the hemolytic type has been shown to develop within a period of 2 weeks when sulfanilamide, sulfanilylguanidine, sulfapyridine or sulfathiazole is incorporated in the stock ration. The potentiality of each of these drugs for the production of anemia was related by Richardson (J. Pharmacol. and Exp. Therap., 72, 99, 1941) to the sulfonamide concentration found within the erythrocyte; the 4 sulfonamides were shown to be indistinguishable from one another with respect to the molar erythrocytic concentration required to produce anemia.

In this study, sulfamerazine and sulfadiazine were examined for their capability of producing hemolytic anemia in the mouse; sulfapyridine was used as a standard of comparison.   The sulfonamides were thoroughly incorporated in the stock ration in various concentrations, each of which was given ad libitum to several experimental groups.   Evidence for the production of anemia was obtained from colorimetric determinations of hemoglobin, using the acid-hematin method.

The comparison of the anemia-producing potency of the sulfonamides was based upon the percentage incidence of anemia at various levels of sulfonamide concentration in the blood.   The blood level which produced a 50% incidence of anemia was found to be as follows: sulfapyridine, 2.8 mg. per 100 cc.; sulfadiazine, 33 mg. per 100 cc.; and sulfamerazine,

31 mg. per 100 cc. The actual sulfonamide concentration within the erythrocytes at these levels was: sulfapyridine, 2.5 mg. (10 micromols) per 100 cc.; sulfadiazine, 26 mg. (105 micromols) per 100 cc.; and sulfamerazine, 23 mg. (87 micromols) per 100 cc.

Although Richardson's findings with sulfapyridine have been confirmed, the 2 pyrimidine derivatives, sulfamerazine and sulfadiazine, are productive of hemolytic anemia in the mouse only when the sulfonamide concentration within the erythrocytes is raised to a level approximately 10 times that required for sulfapyridine. Although it is possible that the degree of hemolytic anemia produced in the mouse by a sulfonamide may be related to its concentration within the erythrocyte, it is apparent that the various sulfonamides are not necessarily equivalent in anemia producing potency and that the toxic effect of sulfonamides on erythrocytes is not inherent in the sulfanilamide nucleus. Clinical data so far available suggest that the incidence of hemolytic anemia in man following the use of sulfadiazine or sulfamerazine is lower than with sulfapyridine or sulfathiazole.

Effects of Acute Hemorrhage of Known Amount on the Circulation of Essentially Normal Persons. H. A. Shenkin, R. H. Cheney, S. R. Govons and I. Starr (Departments of Neurosurgery and Research Therapeutics, University of Pennsylvania). A group of 23 essentially healthy volunteers has been bled amounts which varied from 500 to about 1000 cc. Observation of pulse rate and blood pressure were made, before and for several hours after hemorrhage, in both the recumbent and erect positions; and ballistocardiograms were taken in the recumbent position. When the amount bled was over 500 cc. the blood drawn was eventually replaced and observations made after its restoration. The blood was drawn from the antecubital vein in from 4 to 20 minutes.

Hemorrhages up to 1000 cc. produced only slight changes of blood pressure, pulse rate and ballistocardiographic record as long as the subjects remained recumbent. The values obtained were usually well within the normal range, so that in the great majority of cases it would have been impossible to diagnose the hemorrhage, had one not been aware of it, as long as the subjects remained recumbent and at rest.

However after the hemorrhage as soon as the subjects stood upright the pulse rate accelerated and blood pressure fell to a degree far more marked than was found either before the hemorrhage or after the blood was restored, and 8 subjects were unable to stand without collapsing. Such spells of faintness were accompanied by marked slowing of the pulse, sweating, facial pallor, and nausea, which sometimes persisted for several minutes after the subject was laid flat.

Conclusions. Hemorrhage of large amounts could not be diagnosed by the usual clinical methods as long as the subjects were recumbent and at rest. But as soon as the subjects arose, the abnormality became apparent.

A Biological Method for the Quantitative Estimation of Certain Organic Bases. Dorothy R. Stewart and M. H. Jacobs (Department of Physiology, University of Pennsylvania). The method depends on the ability of tannic acid (*a*) to combine with alkaloids and other organic bases, and (*b*) to retard the exchange of ions across the red cell membrane, thereby slowing the course of hemolysis in a suitable mixture of NH_4Cl and NH_4HCO_3.

The pH of a M/6 solution of NH₄Cl is first raised slightly above 7, with an alkaline phosphate buffer and approximately M/600 NH₄HCO₃ and 1/600% tannic acid are added. The times of 75% hemolysis of freshly washed erythrocytes in this mixture are then determined (a) with no addition, (b) with the addition of an unknown amount of the base in question, (c) with the addition of known amounts of the same substance, and (d) with the omission of the tannic acid. To secure speed as well as accuracy, the unknown concentration is adjusted by dilution to give a time of hemolysis 2 or 3 times as great as that obtained with the test solution lacking the tannic acid.

Since tannic acid also combines with proteins, which begin almost immediately to escape in disturbing traces from freshly washed erythrocytes, standardizations and measurements are carried on simultaneously, using 3 tubes at a time, all started at the same instant, the middle one containing the unknown solution and the others one of a higher and one of a lower known concentration respectively. By a series of successive approximations the known solutions are brought to any desired degree of closeness to each other and to the unknown solution.

The method has been tested superficially with quinine and strychnine and carefully with atabrine. With the latter substance concentrations of 1 to 1 million or less can be measured with an accuracy of 2 or 3%.

Respiratory Inhibitions Studied by Analysis of Single Fiber Discharge in the Phrenic Nerve. ROBERT HODES and M. G. LARRABEE (Johnson Foundation, University of Pennsylvania). The superior laryngeal nerve was stimulated centrally in anesthetized cats and the activity in single phrenic motoneurones was recorded by means of an amplifier and cathode-ray oscillograph.

A sharply defined threshold for inhibition of inspiration can be demonstrated by applying different numbers of stimuli during the course of inspiration. With stimulation of less than threshold value, short delays are introduced between successive phrenic impulses, after which inspiration continues to completion. The greater the sub-threshold stimulation applied, the greater is the pause between successive phrenic impulses. Threshold inhibitory stimulation frequently causes a sequence of events consisting of the customary cessation of activity during stimulation followed by escape of 1 to 3 impulses before inhibition becomes complete. This brief resumption of activity may occur following stimulation during the middle or latter part of inspiration but is never seen following stimulation applied immediately after the first impulse of an inspiration.

The threshold for inspiratory inhibition declines progressively during the course of inspiration. Two periods of subthreshold stimulation can sum to inhibit inspiration when separated by as much as 0.4 second.

Brief stimulation during expiration prolongs the expiratory phase.

All the above results can be demonstrated after section of the carotid sinus and vagus nerves.

Inhalation of high CO₂ or low O₂ mixtures raises the inhibitory threshold. The response to high CO₂ remains despite chemoreceptor denervation, but the low O₂ effect is abolished by such a procedure.

All the foregoing results, as well as most other respiratory phenomena can best be explained by employing, with a few additions, the schema of respiratory interconnections proposed by Pitts et al. (1939).

BOOK REVIEWS AND NOTICES

ESSAYS IN BIOLOGY. In Honor of HERBERT M. EVANS. Written by his Friends. Pp. 687; many illus. Berkeley and Los Angeles: University of California Press, 1943. Price, $10.00.

AN examination of this memorial volume, written in honor of Dr. Herbert Evans (including a complete bibliography of his work and 48 essays contributed by his friends and associates) stimulates the reader with thoughts concerning the present status of the individual scientist in the ever widening field of experimental biology. One thinks of the scope of biological research, and that we are all experimental biologists. Thus, an essay "On the Growth of Deer Antlers" is found next to one on the "Heart in Myxedema," and Sigerist's "Impotence as a Result of Witchcraft" precedes H. P. Smith's discussion of the quantitative aspects of blood coagulation.

Then one is reminded of the high degree of specialization to which biology has evolved by the 3 papers dealing with the relation between minerals, Na and K, carbohydrate metabolism and the adrenals, which are written by Jane Russell, Evelyn Anderson, and Irvine McQuarrie.

One might well wonder to what extent an individual might cover such a wide field in the presence of competition to be expected from the highly specialized. A study of Evans' bibliography shows that he worked on problems in anatomy, physiology, nutrition, chemistry, biochemistry, and embryology. Of interest is the fact that he published 19 papers in the first decade of his career, and 22 in the single year of 1942. Tacit implication of far-reaching changes that have taken place is found in the fact that the former papers were published in 11 different journals, while the latter were carried by 9, only 1 of which is among the first list, and most of the 8 remaining were non-existent at the beginning of Evans' researches.

Among the essays are a number of historical papers which are new and refreshing, in that they bring within reach of the reader information concerning which everyone could find quotations but few could actually read. One of these is a translation of Purkinje's "Contributions to the History of the Bird's Egg Previous to Incubation." Here is related that the distinguished scientist was not the first "to suffer the violent disturbance in a university circle when the reflected glimmer of established dignity began to fade in the light of a major luminary."

An article on the forgotten theorems of Carnot brings to light the false premises upon which the law of the conservation of energy was founded. Yet we must not forget that this law was the foundation upon which our knowledge of energy metabolism was based, which today has made it possible for war leaders to calculate the energy requirements of the soldiers in terms as accurate as those used to determine the gallons of gasoline demanded by the engines which drive the machines of modern warfare.

Although there might be few people who can read every essay critically, there is no question but that everyone can find in this volume a number of essays worthy of close attention.   J. S.

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ALLERGY, ANAPHYLAXIS AND IMMUNOTHERAPY. Basic Principles and Practice. By BRET RATNER, M.D., Clinical Professor of Pediatrics, New York University College of Medicine; Visiting Pediatrician and Director of Pediatrics, Sea View Hospital, etc. Pp. 824; 88 illus.; 56 tables. Baltimore, Md.: The Williams and Wilkins Company, 1943. Price, $8.50.

THERE is no phase of clinical medicine now untouched by the ever widening field of allergy at one time or another. Modern treatment of infectious dis-

eases is based more than ever before on the principles of immunology. The problems of immunotherapy are inseparably linked with those of allergy and no internist can afford to be ignorant of their basic principles.

Dr. Ratner has carried on extensive laboratory and clinical studies in this field and has produced a book of incalculable value. He indicates the insidious ways in which allergic sensitization may be acquired and points out the dangers of indiscriminate serum and sulfonamide therapy. The uses of vaccines, toxoids, blood transfusions, and blood substitutes, are also presented in minute detail. The text proceeds from descriptions of materials and methods of their preparation to the details of immunotherapy in the major disease entities. In its latter portion there is a complete discussion of allergy to immunotherapeutic agents which also includes the principles of allergy in general. The subject matter is well presented. The illustrations are complete and satisfactory. In short, it is a work which should prove invaluable to the internist in general, but particularly to the allergist and immunologist.

M. M.

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HUMAN NEUROANATOMY. By OLIVER S. STRONG, Formerly Professor of Neurology and Neurohistology, College of Physicians and Surgeons, Columbia University, and ADOLPH ELWYN, Associate Professor of Neuroanatomy, College of Physicians and Surgeons, Columbia University. Pp. 417; 320 figures. Baltimore: Williams & Wilkins Company, 1943. Price, $6.00.

DESIGNED primarily for students, this text is sufficiently complete and detailed to obviate the student's need of any larger references and to be of value to many physicians. Neuroembryology, neurohistology, and the peripheral nervous system are discussed in the first 80 pages and are followed by a systematic description of the central nervous system, with pertinent data on functional changes, with "judicious repetition," and with frequent coördination of the new facts with those already learned by the student. Illustrations are abundant, well done, and interspersed with the text. Frequent usage of a photograph with an adjacent diagram of the identically same region adds to the clarity of presentation. This volume is well done, up to date, and equal, at least, to any in this field.

M. F.

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TEXTBOOK OF ANATOMY AND PHYSIOLOGY FOR NURSES. By CARL C. FRANCIS, A.B., M.D., Senior Instructor in Anatomy, Department of Anatomy, Western Reserve University, Cleveland; G. CLINTON KNOWLTON, PH.D., Assistant Professor of Physiology, College of Medicine, State University of Iowa; and W. W. TUTTLE, PH.D., Professor of Physiology, College of Medicine, State University of Iowa. Pp. 586; 338 illus. (38 color plates). St. Louis: C. V. Mosby Company, 1943. Price, $3.50.

THIS new anatomy and physiology textbook intended for student nurses is more compact than the usual text of this kind. It is clearly written and well illustrated with photographs, color plates, and pertinent descriptions.

The subject matter is arranged in units which are not wholly in accord with the pattern suggested in the 1937 Curriculum Guide for Schools of Nursing. Generally speaking, chapters follow one another in logical sequence with the exception of the chapter on "Nutrition and Metabolism" which may prove confusing to those students who have not yet studied the digestive system. Superimposed photographs of exceptional clarity and many detailed illustrations make the sections on articulations, muscles, and nerves of especial value to both student and teacher of anatomy and physiology.

Despite occasional minor errors in terminology and labeling of diagrams which indicate the need for more careful editing, this Reviewer has found the book adequate as a text for teaching, and excellent as a reference book for student nurses. Suggestions which may improve its teaching merits are; summaries of the most important facts at the end of each system, and more practical applications of and references to the actual nursing situations which the student will encounter.

H. F.

PICTORIAL HANDBOOK OF FRACTURE TREATMENT. By EDWARD L. COMPERE,
M.D., F.A.C.S., Associate Professor of Surgery, Northwestern University
Medical School; Chairman, Department of Orthopædic Surgery, Wesley
Memorial Hospital; Consulting Orthopædic Surgeon, Chicago Memorial
Hospital; and SAM W. BANKS, M.D., Associate in Surgery, Northwestern
University Medical School; Attending Orthopædic Surgeon, Chicago Memo-
rial Hospital. Pp. 351; 171 figs. Chicago: Year Book Publishers, 1943.
Price, $4.25.

THE entire field of fracture treatment is covered in an exceedingly brief,
terse, and pithy style. Controversial points are strictly avoided, and only one
method of treatment is described for each type of fracture. An abundance of
small, lucid, straight-to-the-point drawings and roentgenographs assist in
making this small volume useful to the general practitioner who is forced by
necessity of location to treat fractures, and who often is obliged to learn the
"simple facts" in some haste.   M. F.

PAPERS FROM THE SECOND AMERICAN CONGRESS ON GENERAL SEMANTICS.
Non-Aristotelian Methodology (Applied) for Sanity in Our Time. Com-
piled and Edited by M. KENDIG. Pp. 581. Chicago: Institute of General
Semantics, 1943. Price, $5.00.

SINCE the publication in 1933 of Alfred Korzybski's "Science and Sanity:
An Introduction to Non-Aristotelian Systems and General Semantics," which
may be taken as launching the Semantics movement, this discipline has made
steady if not conspicuous progress. The founding of the Institute of General
Semantics in Chicago in 1938 and a General Congress has now been followed
by the Second American Congress on the subject in July 1943; under the
Presidency of Franklin Ebaugh, M.D., of the University of Colorado.

This stout volume includes over 80 papers divided into 2 books. The first
and shorter, which deals with Non-Aristotelian Orientations and the Method-
ology with Related Subjects, presents, inter alia, a historical introduction by
O. L. Reiser and general discussions by Korzybski and Adolf Meyer. The
reader who is not familiar with the theory and terminology of General Seman-
tics will find them briefly explained in Korzybski's 17-page paper (p. 93).

The lengthier Book 2, on Human Adjustment, is concerned with the newer
approaches to such far-flung subjects as Neuropsychiatric Foundations, Medi-
cal Education and Practice, Physiotherapy, Stuttering, Vision, Dental Caries,
Nutrition, Mental Hygiene, Marital Counseling, Pathology, behaviorism and
so on. One might reasonably question how closely such subjects are related
to Semantics and in fact examination shows that in many it either plays a
small and unnecessary rôle or does not appear at all, the topic thus being
treated as it would be at any professional meeting—and some not too well
treated at that.

Semantics is basically concerned with language. The word, coined by Bréal
in 1897 from the Greek, "significant" is used mostly in the sense of the mean-
ing of words and their significance. One is not surprized, therefore, to find a
number of papers on such topics as language, public speaking, movies, journal-
ism, teaching of English, and so on. It is in such fields that Semantics can
first bring practical results. Old Aristotle as usual comes in for some hard
knocks, mostly undeserved; but he doubtless can take these and is glad to do
so if knowledge is advanced thereby. Better knowledge of the true meanings
of words and their significances, added to a conscientious use of this knowledge,
would remove much unnecessary confusion in scientific and other discussions,
much of the illegitimate and harmful effects of propaganda, advertising,
broadcasting, and other evils peculiar to the present day. Shakespeare's
mellifluous response to his own query "What's in a name?" (a "purr" Seman-
ticism, incidentally) is much less valid than Socrates' axiom: "I have no
objection to your giving names any significance that you please if you will
only tell me what you mean by them."

Semantics, being necessarily a subject that deals in many abstractions and

tends to attract theorists and those who deal in or fall for "hot air," the pilots and well-wishers of the movement would do well to see that its more vocal followers keep their feet on the ground as well as Nature permits and that those wanting to ride on the bandwagon are not permitted to twist a valuable concept unsemantically to suit their selfish purposes.   E. K.

DIAGNOSIS OF UTERINE CANCER BY THE VAGINAL SMEAR. By GEORGE N. PAPANICOLAOU, M.D., PH.D., Department of Anatomy, Cornell University Medical College, New York; and HERBERT F. TROUT, M.D., Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital. Pp. 46; 11 colored plates. New York: The Commonwealth Fund, 1943. Price, $5.00.

IN this monograph are embodied the results of routine vaginal smear examinations from 3014 women, most of whom were in the cancer-bearing age. It entails "probably between 7000 and 10,000" smears. Of the 179 patients found to have primary cancer of the uterus, 127 were from the cervix and 53 from the fundus. Of the 127 cervical lesions, failure to detect the malignant cells in the smears occurred 4 times; in the 53 fundic lesions it occurred 7 times. An analysis of these failures revealed that most cases were either post-irradiational or were patients with adenoma malignum. In several instances the authors suspected malignant disease before one or more biopsies confirmed it. The authors emphasize that the vaginal smear method is not recommended as a means of ultimate diagnosis, but to be confirmed by biopsy, since the evaluation of individual cells is a much more difficult task than the recognition of cancer in tissue preparations. In view of the surprisingly high accuracy of diagnoses of these men, the ease of obtaining smears and the relatively simple technical procedure combine to form a seemingly valuable diagnostic as well as follow-up method for the gynecologist and pathologist. It is also apparent that the use of this method is of value only in the hands of those thoroughly familiar and experienced in cytologic detail in isolated and clumped cells arising from an area so richly endowed with varying cell types. The text is devoted largely to describing the types of cells found in vaginal smears under various physiologic and pathologic conditions, and these are illustrated by excellent colored camera lucida drawings and microphotographs.
                    M. T.

BORDERLANDS OF PSYCHIATRY. By STANLEY COBB, M.D., Bullard Professor of Neuropathology, Harvard Medical School; Psychiatrist in Chief, Massachusetts General Hospital. Pp. 166; 27 figs. Cambridge, Mass.: Harvard University Press, 1943. Price, $2.50.

IN this Fourth Harvard University Monograph in Medicine and Public Health, the author is concerned with a somewhat neglected 6½ million persons who are partially incapacitated. The chapter on "Body and Mind" with its 5 case histories shows the fallacy of the terms functional or organic, mental or physical, since "every symptom is both functional and organic." In the section on "Parallel Evolution of Speech, Vision and Intellect," it is asserted that at birth both cerebral hemispheres appear equipotential, but through inheritance the learning process tends to be unilateral; through the special senses symbolic meanings develop and these are correlated into language. "Speech and Language Defects" show that the former is probably "the most integrated and sensitive of the human functions. . . . it normally and abnormally is affected by many stimuli." Accordingly, the collaboration of different specialists is required to solve the problem of stammering. "Functions of the Frontal Area" suggest the undesirability of removing a portion of the brain, thereby rendering "the patient lazy and indiscriminating . . . . in order to make the patient happier." "The Anatomical Basis of Emotions" speaks of the hypothalamus not as a "center of emotion" of feeling, but as "a motor

way-station where emotion is integrated into behavior patterns . . . ." But emotion may "take place in a rudimentary way in the thalamus of man, and in a much more discriminative way in the cerebral cortex." In "Consciousness," the varying depths of sleep are studied through electrograms. Levels of wakefulness range from mania to stupor. It is suggested that later, consciousness may be described in terms of electrotonic activity. Concerning "Fits," the functional abnormalities of epilepsy are described as "(1) *changes in electrical potentials as seen in the electro-encephalogram; (2) changes in consciousness; (3) nervous discharge into smooth muscle, striated muscle, or glands, causing involuntary visceral or motor behavior.*" Psychoneurosis admittedly is a difficult condition to define and measure. It has been described as "a personality disorder severe enough to cause the patient to seek medical advice or be advised to seek help." There are estimated to be 2,500,000 psychoneurotics in the country. "Psychosomatics" is a new term but not a new condition. In 1907, Kreibich, a German, reported the induction of a blister on the skin through hypnosis. More extensive lesions have been induced and it is argued that such phenomena may probably occur in tissues less accessible to scrutiny. These disorders are said to be concerned largely with emotions, feelings, autonomic neurology, and related medical symptoms, including hysteria.

Though a book of such miscellaneous contents is one of essays rather than a monograph, with rare discrimination and skill, the author has painstakingly presented much illuminating material.   N. Y.

CHEMICAL SPECTROSCOPY. By WALLACE R. BRODE, Professor of Chemistry, Ohio State University. Second Ed. Pp. 677; 1 colored plate; numerous illus., spectrum tables and charts. New York: John Wiley & Sons, Inc., 1945. Price, $7.50.

THIS edition of Brode's text follows the general plan of the first edition. Revision, except for the inclusion of spectrum tables with relative intensities of lines based upon the data of G. R. Harrison (M. I. T.), has not been extensive.

The text is well written, and provides a readable, useful summary of information upon various types of spectroscopic equipment. The spectrum tables and charts, wisely relegated to a separate section of the book, will be useful for reference.

The work is intended for the chemist and chemical student who desire to use spectroscopy as an analytical tool. While absorption spectra are perhaps adequately treated, this phase of the subject could have been somewhat expanded to render the book more useful to students of medicine and biology.

The general excellence of the text is such that the Reviewer regrets that such factors as "errors" and "limitations" of technique have not been adequately treated. From the standpoint of the student, it might have been preferable also to present in more critical detail the use of a small number of representative instruments, rather than to furnish a general account (as the author has done) of a large variety of equipment.

This text is recommended as a worthwhile work which provides a panoramic view of the field it covers.   D. D.

THE BOY SEX OFFENDER AND HIS LATER CAREER. By LOUIS J. DOSHAY, M.D., Psychiatrist, Children's Courts, New York City; Formerly Senior Assistant Physician, Manhattan State Hospital, New York, and Assistant Specialist in Neuropsychiatry, U. S. Veterans Hospital, New York. Foreword by GEORGE W. HENRY, M.D. Pp. 206; 40 tables, 12 diagrams. New York: Grune & Stratton, Inc., 1943. Price, $3.50.

NOT knowing of any similar work, the author has sought to determine what bearing sexual delinquencies of boys ranging from 7 to 16 years, has had upon

their lives between the ages of 16 and 28.   Feebleminded boys and all girls
were excluded.   While boys commit many non-sexual offenses, those of girls
are usually sexual—"a different set of motivations and dynamics is involved."
Two important groups were considered: those showing sexual offenses exclu-
sively, and those delinquent in a mixed sense—thievery, truancy, etc., included.
The commonest offenses were: "lewdness, voyeurism, excessive masturbation,
exhibitism, fornication, assault, incest, active and passive perverted practices
with juveniles or adults of the same sex."   In the total of 256 subjects, delin-
quencies were shown as not due to disparity in ages of the parents.   The find-
ing of only 4% with glandular defects shows the fallacy in believing endocrine
dysfunction a contributor to much criminality.   Except for incest with sisters,
"so-called good boys commit just as many violent sexual offenses as the con-
firmed delinquent, indicating that forecast and treatment ought not rest on
the sex offense alone."   Orthodox psychoanalysis is interdicted since "the
long-drawn-out procedure and the inevitable emphasis on the original sex
offense, is diametrically opposite to the needs of the case."   Given appropriate
court and clinic treatment, it is believed these delinquents tend to be cured
automatically.   This valuable and stimulating study includes much statistical
matter.   N. Y.

THE RÔLE OF NUTRITIONAL DEFICIENCY IN NERVOUS AND MENTAL DISEASE.
   Vol. XXII.   Proceedings of the Association, Dec. 19 and 20, 1941, New
   York.   Editorial Board: STANLEY COBB, M.D., Chairman; EDWIN F.
   GILDEA, M.D., HARRY M. ZIMMERMAN, M.D.   Pp. 215; 23 illus., 8 tables.
   Baltimore: Williams & Wilkins Company, 1943.   Price, $4.00.

THIS most recent volume in the series annually issued by the Association
for Research in Nervous and Mental Disease is considerably reduced in size,
unquestionably due to the turning of the medical profession to problems of war.
The contributions are divided into those from the fundamental sciences and
those from clinical research.
   Among the former is a concise review of the relationship of enzymes to
nutritional deficiencies by C. A. Elvehjem.   It is, of necessity rather technical,
but sufficiently clear and elementary to plot the course this field has traversed
in research, and to give the direction for further progress.   H. E. Himwich
presents the biochemical advances of recent years in the relationship of thiamin
and nicotinic acid to cerebral metabolism.   The pathology of the vitamin B
group deficiencies by H. M. Zimmerman provides the high water mark of this
volume.   The material for this review is largely Dr. Zimmerman's personal
work, and this symposium provided an opportunity to summarize, correlate
and evaluate the pathologic changes of vitamin B group deficiencies as found
in man with the changes produced experimentally in animals.   A most informa-
tive review of the effects of vitamin E deprivation in various laboratory animals
is presented by A. M. Pappenheimer.   Other articles in the first portion of the
volume are by Dr. Cowgill (principles of research in nutrition); Drs. Wolbach
and Bessey (the mechanical relationship of vitamin A deficiency and the cen-
tral nervous system in the immature animal); Ferrebee, Weissman, Parker
and Owen (thiamin content of human tissue).
   Outstanding contributions of clinical research are by Wilder and by Spies,
Bradley, Rosenbaum and Knott, emphasizing the psychologic disturbances
resulting from thiamin deficiency.   These controlled studies demonstrate that
the earliest evidences of thiamin deficiency are in the emotional sphere and
that mental disturbances in pellagrous patients should be considered as prob-
ably partially composed of a thiamin deficient element and not completely
attributed to niacin deficiency.   A review of the mental and neurologic aspects
of thiamin, niacin and pyridoxine deficiencies by W. H. Sebrell rounds out this
phase of the problem.
   In a review of multiple neuritis, M. B. Streuss again points out that thiamin
deficiency is probably not the only factor in polyneuritic changes, and nutri-
tional polyneuritis should be treated by other nutritional factors as well as

with thiamin. Other multiple neuritides are discussed and differentiated from nutritional polyneuritis. Other clinical contributions include an article on psychiatric syndromes caused by nutritional deficiency by Bowman and Wortis, which comprehends a discussion of delerium tremens, Korsakoff's syndrome and Wernicke's disease. Evidence is presented from blood pyruvate studies that the latter is definitely associated with thiamin deficiency.

In spite of these many important contributions, however, this volume is not up to the previous standards of the Society.   H. S.

AIR-BORNE INFECTION. By DWIGHT O'HARA, M.D., Professor of Preventive Medicine, Tufts College Medical School; Visiting Physician, Boston City Hospital; Physician-in-Chief, Waltham Hospital. Pp. 114; several charts and tables. New York: The Commonwealth Fund, 1943. Price, $1.50.

THE author unveils an interesting sketch of the problem of air-borne infections as seen through the eyes of a student of preventive medicine. While not entirely ignoring the contact rôle of infection, Dr. O'Hara merely side-steps the issue for he is interested mainly in the air-borne phases of such diseases as smallpox, diphtheria, the common cold, pneumonia, streptococcus infections, tuberculosis and others.

Since 1900 there has been a definite decrease in the mortality rates of such diseases. The author attempts to probe out the causes and presents his observations on the decline of air-borne infection.

Among his conclusions he states that the greatest contribution in the improvement of our respiratory health between 1918–1938 has been made by the hygienists and sanitarians in what he describes as a better "living standard." The author does not give entire credit to them, however, for he also discusses the rôle of accepted preventive measures, immunization, decreased virulence, advanced therapeutic measures, strengthened resistance and reduced concentration of atmospheric infection, as well as the isolation of infecting sources. Each and all have had a part in the rapid decrease of air-borne infections.

This book could be read to great advantage by every practitioner and public health officer, for it contains good discussions and observations of the truths underlying the decline of air-borne infections.   F. E.

MEDICAL CLINICS OF NORTH AMERICA. Symposium on Physical Therapy, Mayo Clinic Number, July 1943. Pp. 317; many illus. Philadelphia: W. B. Saunders Company. Price, year $16.00.

THIS symposium includes 20 articles by members of the Staff of the Mayo Clinic and by medical officers of both services stationed there. The principles and techniques of physical medicine applicable to arthritis, vascular diseases, poliomyelitis (the Kenny treatment), backache and other problems are discussed for both hospital and ambulatory patients. Simple methods and devices for home use are stressed. The management of common war disabilities by physical and also occupational therapy are adequately considered. This issue is to be recommended because a careful attempt has been made to evaluate and present the best of the current methods in this field of ever-growing usefulness.   R. H.

THE MICROSCOPE AND ITS USE. By FRANK J. MUÑOZ, Technical Microscope Consultant; in Collaboration with DR. HARRY A. CHARIPPER, Professor of Biology, New York University. Pp. 334; 122 figs. Brooklyn, N. Y.: Chemical Publishing Company, Inc., 1943. Price, $2.50.

THE book is preëminently "popular," and in effect consists of chapters which serve as introductions to the microscope (and its many accessories, such as lighting fixtures, mechanical stages, counting chambers, demonstration ocu-

lars, photomicrographic cameras, etc.), the metallurgic microscope, and the polarizing microscope. The authors go beyond the information usually contained in pamphlets provided by manufactures, and discuss rather technical subjects such as "numerical aperture," Kohler illumination, resolution, and so forth, in a simplified language, although adequate for those who will find this book of value. The glossary is helpful. A small bibliography introduces the reader to several valuable references.

The text will be useful as an introduction to the equipment available for fields in which the microscope is employed.

E. W.

PRINCIPLES AND TECHNIQUES OF NURSING PROCEDURES. By SISTER MARY AGNITA CLAIRE DAY, St. Louis University School of Nursing. Pp. 574; 94 illus. St. Louis: C. V. Mosby Company, 1943. Price, $3.50.

THIS book is a compilation of nursing practices as developed in St. Mary's Group of hospitals of St. Louis University. The text constitutes a good procedure book. The organization of material follows to some extent the plan set forth in the Curriculum Guide for Schools of Nursing. Each procedure is headed by a brief discussion of its underlying principles, indications and contraindications, and other factors which seem essential to understanding. The book eliminates unnecessary duplication of material which is discussed in detail in other courses. If the text is used only as a procedure book, it may prove satisfactory; however, more consideration should be given to the philosophy of education and the psychology of learning processes. There is a dearth of correlation between the principles and practices of nursing and their underlying sciences. Little import is given to the nurse as a teacher of hygiene and preventive medicine. The procedures, however, are simple and are adaptable to both home and hospital situations.

N. Y.

AN INTRODUCTION TO CLINICAL PERIMETRY. By H. L. TRAQUAIR, M.D., R.F.R.C.S. (ED.), Ophthalmic Surgeon, Royal Infirmary, Edinburgh; Ophthalmic Surgeon, Charles Chalmers Hospital, Edinburgh; Oculist to the Edinburgh Municipal Hospitals; Lecturer on Diseases of the Eye, Edinburgh University. Fourth ed. Pp. 332; 245 illus.; 3 colored plates. London: Henry Kimptom, 1942. Price, $6.50.

TRAQUAIR continues the outstanding book on perimetry. A few illustrations have been added. There have been surprisingly few changes or additions to the text. War conditions have appreciably changed the format, in that the cover, binding and paper are inferior. On the other hand, the smaller size of the book makes for easier use.

A. C.

VICTORIES OF ARMY MEDICINE. Scientific Accomplishments of the Medical Department of the United States Army. By EDGAR ERSKINE HUME, Colonel, Medical Corps, United States Army. Pp. 250; 42 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1943. Price, $3.00.

IN wartime days, when the medical effort of the whole country is so largely devoted, directly or indirectly, toward military medicine, it is both especially appropriate that this book should appear, and fortunate that it should come from the pen of such an experienced writer and distinguished physician as Colonel Hume. One's hopes are not disappointed. Walter Reed's demonstration of the mode of yellow fever transmission and Beaumont's contribution to knowledge of gastric digestion are so well known to everyone that they have been treated here with commendable brevity. But other less well known, important contributions of the United States Army Medical Department furnish the material for the bulk of the volume.

The 14 well-balanced chapters first sketch in 45 pages the course of the U. S. Army Medical Department since 1775. Then follow descriptions of "Three great American Medical Institutions" (the Army Medical Library and its Index Catalogue, the Army Medical Museum, the Army Medical School); Anthropology; Ornithology; the Army's gift to Surgery, and the Reed and Beaumont chapters. Changing to a chronologic approach, the advances during and between four war periods are described in as many chapters, the two final chapters disposing of various miscellaneous items.

As in any good history, the Reference section is copious and the Index adequate.

Colonel Hume has amply proved his thesis that United States Army medical officers have made their share of worthy contributions to medical science. The medical profession as a whole should certainly read this book and become better acquainted with the achievements of their Army Medical Department, while the thousands now on active service undoubtedly will want to know more about its distinguished past.   E. K.

SYNOPSIS OF TROPICAL MEDICINE. By SIR PHILIP MANSON-BAHR, C.M.G., D.S.O., M.D., F.R.C.P., Senior Physician to the Hospital for Tropical Diseases, Royal Albert Dock and Tilbury Hospitals; Consulting Physician in Tropical Diseases to the Dreadnought Seaman's Hospital, London; Director, Division of Clinical Tropical Medicine, London School of Hygiene and Tropical Medicine; Consulting Physician to the Colonial Office and Crown Agents for the Colonies; Consultant in Tropical Medicine to the Admiralty and to the Royal Air Force; Lumleian Lecturer, Royal College of Physicians, 1941. Pp. 224; 5 plates. Baltimore: Williams & Wilkins Company, 1943. Price, $2.50.

THE author of this book is the well-known authority on tropical medicine who has so successfully edited the many editions of "Manson's Tropical Diseases." The text seems to be a condensed version of the larger volume, with contents rearranged into what strikes this Reviewer as a more logical sequence. To accomplish this degree of condensation and still maintain reasonable completeness, the author has resorted to telegraphic style, outlines and abbreviations wherever possible. The result is a pocket-size book containing the essential facts. It should have wide usefulness for many years.
                                                                    H. R.

REHABILITATION OF THE WAR INJURED. A Symposium. Edited by WILLIAM BROWN DOHERTY, M.D., and DAGOBERT D. RUNES, PH.D. Pp. 684; many illus. New York: Philosophical Library, Inc., 1943. Price, $10.00.

THE editors and publishers of this work have rendered an important service to the war effort by assembling in one volume the writings of outstanding authorities in many fields on subjects pertaining to rehabilitation of military casualties. The main sections cover Neurology and Psychiatry, Reconstructive and Plastic Surgery, Orthopedics, Physiotherapy, Occupational Therapy and Vocational Guidance, and Legal Aspects of Rehabilitation. The principal usefulness of this book will be to inform those engaged in planning for rehabilitation as to what can be accomplished by specialists in the several fields of medicine. No book of this length and covering so many fields could be adequate for the needs of the specialist himself, but such is not the editors' intent. The volume is specifically recommended to the personnel of the military departments of the armed services, particularly those of policy-making rank, so that they may judge for themselves as to the adequacy of the treatment being provided to war casualties for whom they are responsible.

One half of the 54 articles are provided with bibliographies of varying completeness. It is regrettable that the authors were not all required to provide complete bibliographies, because the value of the work would thereby have been greatly enhanced.   J. L.

DICTIONARY OF BIOCHEMISTRY AND RELATED SUBJECTS. Editor-in-Chief, WILLIAM MARIAS MALISOFF, Professor of Bio-Chemistry at the Polytechnic Institute of Brooklyn. Pp. 579. New York: Philosophical Library, Inc., 1943. Price, $7.50.

THE Editor-in-Chief explains that "The dictionary contains a great deal of glossary material, and also a great deal of fairly lengthy authoritative discussion. It tried to maintain a balance between obsolescent, established and newly explored material. It is designed for readers of biochemical literature who might want the definition of terms used more than a decade ago as well as of terms just coined."

Forty-six collaborators have aided in compiling approximately 10,000 definitions of biochemical terms. Some 50 items receive from 1 to 17 pages of authoritative discussion—thus accounting for approximately one-half of the volume. Many of the articles are well documented with references.

Relatively few errors have been found, though some definitions appear inadequate. Some quotations have not been given with their proper content.

The Editor should be congratulated upon this attempt in designing a dictionary in this field. It should be very useful to the student of "biochemistry" and to workers in related fields. H. V.

MEDICO-LEGAL BLOOD GROUP DETERMINATION. Theory, Technique, Practice. By DAVID HARLEY, M.D., B.Sc., F.I.C., The Laboratories of the Inoculation Department, St. Mary's Hospital, London. Pp. 119; 13 figs.; 23 tables. London: William Heinemann. Distributors in U. S. A., Grune & Stratton, Inc., New York, 1943. Price, 12s 6d.

THE application of Blood Group determinations to forensic medicine constitutes an advance in scientific legal investigation. The lag in the acceptance by the courts in this country of blood group determinations as admissible evidence, and the lack of legislation authorizing the court to order such examinations make it particularly important that every possible means of spreading information on the subject among both legal and medical practitioners of all kinds be available. In this respect, we are far behind the medico-legal practice of many countries on the Continent, Russia and Japan.

In this volume, the theory of blood groups, their hereditary character, techniques for their determination in blood, and in stains of blood, saliva and semen, are discussed in detail. The possibilities and the limitations of the evidence to be obtained from such examinations are presented.

A number of cases are cited to demonstrate how evidence may be obtained from the examination of blood and of stains of various kinds. Such sections on the need for the test in the civil courts in the determination of non-paternity is excellent. E. W.

AN INTRODUCTION TO SOCIOLOGY AND SOCIAL PROBLEMS. By DEBORAH MACLURG JENSEN, Instructor in Sociology and Social Problems at the Schools of Nursing of St. Louis City Hospital and St. Luke's Hospital; Lecturer in Nursing Education, Washington University. Second ed. Pp. 420; 78 figs. St. Louis: C. V. Mosby Company, 1943. Price, $3.25.

LIMITED in scope to the needs of the student nurse, Mrs. Jensen's textbook introduces the more elementary concepts of sociology and presents social problems that the nurse is likely to encounter in our immediate culture.

The text has been arranged to coincide accurately with suggestions given in the *Curriculum Guide for Schools of Nursing* and has been revised to include social changes that may arise from the present war. Written with clarity and insight, it is keyed to the gait of the average nursing school student. Helpful features are arresting picture graphs, widely chosen bibliographies, and thought provoking questions for discussion at the end of each chapter.

It is the Reviewer's opinion that supplemented with references as suggested this would make an exceptionally good nursing text in sociology. H. F.

ROENTGENOGRAPHIC TECHNIQUE. By DAMON A. RHINEHART, A.M., M.D., F.A.C.R., Professor of Roentgenology and Applied Anatomy, School of Medicine, University of Arkansas; Roentgenologist to St. Vincent's Infirmary, Missouri Pacific Hospital, and the Arkansas Children's Hospital, Little Rock. Third ed. Pp. 471; 201 engravings. Philadelphia: Lea & Febiger, 1943. Price, $5.50.

THIS text is filling an important field in radiology. Diagnostic radiology is undergoing many improvements and the author, through his revisions, has kept his text up to date and, therefore, keeps his readers informed. In this new edition, the author has revised the text thoroughly in the fields where there have been advances in roentgenographic technique. The paper is good, the print is easy to read, and the illustrations are excellent; throughout, the author has used negative illustrations. This is very important because many technicians have difficulty in transposing positive illustrations to what they see on the roentgenograms. The book should be in every department where radiology is done.   E. P.

INJURIES OF SKULL, BRAIN AND SPINAL CORD. Edited by SAMUEL BROCK, M.D., New York University. Second ed. Pp. 616; 78 figs. Baltimore: Williams & Wilkins Company, 1943. Price, $7.00.

THIS symposium on injuries to the central nervous system edited by Dr. Brock contains relatively few changes from the first edition. Many chapters have been rewritten but little material has been added.

The precise details on the methods of administration and the place of sulfonamides in cases of open cranial trauma even now is not fully agreed upon; nevertheless, the data introduced into this new edition, on this most important subject, appears to be inadequate.

The outstanding difference from the first edition is the inclusion of a chapter on the electroencephalogram in cases of head trauma by Paul F. A. Hoefer. This chapter contains observations both electroencephalographically and clinically on a large series of cases, presented in the form of many tables. The place and value of electroencephalography in cranial trauma however is not clearly presented. The article has more of the tone of a statistical report in a journal publication than a chapter in a text or reference volume.

An adequate discussion on the controversial subject of the treatment of closed cranial trauma is still lacking in this new edition. Certainly this subject deserves fuller consideration of the rationales guiding the many opposing views on therapy. Unfortunately the chapter on concussion and contusion of the brain was not revised and a consideration of the important work of Denny-Brown and Russell on the place of acceleration in the physiology of cerebral trauma—a milestone in this field—failed to be included.

This book remains, despite the above criticisms, the best on the subject and continues to be invaluable to the profession in the understanding and handling of central nervous system injuries, both medically and legally.   H. S.

NEW BOOKS

Clinical Diagnosis by Laboratory Examinations. By JOHN A. KOLMER, M.S., M.D., Dr.P.H., Sc.D., LL.D., L.H.D., F.A.C.P., Professor of Medicine in the School of Medicine and the School of Dentistry of Temple University; Director of the Research Institute of Cutaneous Medicine; Formerly Professor of Pathology and Bacteriology in the Graduate School of Medicine of the University of Pennsylvania. Pp. 1239; 75 figs. New York and London: D. Appleton-Century Company, Inc., 1943. Price, $8.00.

Tifus Exanthemático. Etiología—Clínica—Profilaxis. By PROF. DR. G. CLAVERO and DR. F. PÉREZ GALLARDO. Prólogo del PROF. DR. J. A. PALANCA. Gráficas Afrodisio Aguado, S. A.—Bravo Murillo, 31., Madrid. 1941.

Barometric Pressure. Researches in Experimental Physiology. By PAUL BERT. Translated from the French by MARY ALICE HITCHCOCK, M.A., Formerly Professor of Romance Languages at the University of Akron; and FRED A. HITCHCOCK, PH.D., Associate Professor of Physiology at The Ohio State University. Pp. 1055; 23 tables; 89 figs. Columbus, Ohio: College Book Company, 1943. Price, $12.00.

A Clinical and Experimental Investigation of the Blood Cholesterol Content in Myxœdema and Other Conditions. By E. H. STOKES, M.B., CH.M. (SYDNEY), F.R.A.C.P., Senior Honorary Assistant Physician, Sydney Hospital; Tutor and Honorary Lecturer in Medicine, University of Sydney. Accepted as a thesis for admission to the degree of Doctor of Medicine in the University of Sydney. Pp. 121; 13 figs.; 12 tables. Sydney, Australia: Australasian Medical Publishing Company, Ltd., 1941. No price given.

Biomicroscopy of the Eye. Slit Lamp Microscopy of the Living Eye, Vol. 1. By M. L. BERLINER, M.D., Assistant Professor of Clinical Surgery (Ophthalmology), Cornell University Medical College; Associate Attending Surgeon, New York Hospital; Assistant Surgeon, New York Eye and Ear Infirmary; Instructor in Biomicroscopy, Post-Graduate School, New York Eye and Ear Infirmary; Senior Associate Attending Ophthalmologist, Beth Israel Hospital, New York. Pp. 709; 512 illus. (40 pages color plates). New York and London: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1943. Price, $17.50.

Investigación del Virus Tifoexanthemático en las Ratas de España. By DR. G. CLAVERO and F. PÉREZ GALLARDO. Publicaciones de la Revista de Sanidad e Higiene Publica. May, 1943. Madrid.

La Prueba Intradérmica de Giroud en la Infección Tifoexanthemática. By G. CLAVERO and F. PÉREZ GALLARDO. Publicaciones de la Revista de Sanidad e Higiene Publica. December, 1942. Madrid.

Finger Prints, Palms and Soles. An Introduction to Dermatoglyphics. By HAROLD CUMMINS, PH.D., Professor of Microscopic Anatomy, Tulane University, School of Medicine; and CHARLES MIDLO, M.D., Associate Professor of Microscopic Anatomy, Tulane University (Formerly Assistant Professor of Anatomy, Louisiana State University). Pp. 309; 149 illus. Philadelphia: Blakiston Company, 1943. Price, $4.00.

Biological Symposia. Edited by JAQUES CATTELL, Editor of "The American Naturalist" and "American Men of Science." Vol. X. Frontiers in Cytochemistry. Pp. 334; several figs. Lancaster, Pa.: The Jaques Cattell Press, 1943. Price, $3.50.

The Biochemistry of Malignant Tumors. By KURT STERN, M.D., Formerly Research Associate of the University of Vienna, New York City; and ROBERT WILLHEIM, M.D., Professor, University of Philippines, Manila. Pp. 951. Brooklyn, N. Y.: Reference Press, 1943. Price, $12.00.

Urological Diseases of Pregnancy. By E. GRANVILLE CRABTREE, M.D., Urologist to the Boston Lying-In Hospital. With a signed chapter by GEORGE C. PRATHER, M.D., Assistant Urologist to the Boston Lying-In Hospital. Pp. 472; 158 figs., several in color. Baltimore: The Williams & Wilkins Company, 1942. Price, $5.00.

Electronic Interpretations of Organic Chemistry. By A. EDWARD REMICK, PH.D., Assistant Professor of Chemistry, Wayne University, Detroit. Pp. 474. New York: John Wiley & Sons, Inc., 1943. Price, $4.50.

A Surgeon's World. An Autobiography. By MAX THOREK, M.D. Pp. 410. Philadelphia and New York: J. B. Lippincott Company, 1943. Price, $3.75.

Physiological Psychology. By CLIFFORD T. MORGAN, Associate in Psychology, The Johns Hopkins University; Formerly Faculty Instructor in Psychology, Harvard University. Pp. 623; 176 figs. New York and London: McGraw-Hill Book Company, Inc., 1943. Price, $4.00.

NEW EDITIONS

An Introduction to Clinical Perimetry. By H. M. TRAQUAIR, M.D., F.R.C.S. (ED.), Ophthalmic Surgeon, Royal Infirmary, and Chalmers Hospital, Edinburgh; Oculist to the Edinburgh Municipal Hospital; Lecturer on Diseases of the Eye, Edinburgh University. With a Foreword by NORMAN M. DOTT, M.D., CH.B., F.R.C.S. (ED.). Fourth ed. Pp. 332; 245 illus., 3 colored plates. London: Henry Kimpton, 26 Bloomsbury Way, W. C. 1, 1942. Price, $6.50. (See review in this issue.)

Introduction to Physiological and Pathological Chemistry. By L. EARLE ARNOW, PH.G., B.S., PH.D., M.B., M.D., Director of Biochemical Research, Medical-Research Division, Sharp & Dohme, Inc., Glenolden, Pa.; Professor of Chemistry, Bryn Mawr College Summer School of Nursing, 1941–43; Formerly Assistant Professor of Physiological Chemistry, University of Minnesota Medical School, and Lecturer in Physiological Chemistry to Students enrolled in the University of Minnesota School of Nursing, Minneapolis. Introduction by KATHARINE J. DENSFORD, B.A., M.A., R.N., Director of the School of Nursing and Professor of Nursing, University of Minnesota. Second ed. Pp. 574; 142 figs, 31 tables. St. Louis: The C. V. Mosby Company, 1943. Price, $3.75.

Urine and Urinalysis. By LOUIS GERSHENFELD, P.D., PH.M., D.Sc., Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy and Science. Second ed. Pp. 304; 42 figs. Philadelphia: Lea & Febiger, 1943. Price, $3.25.

Personal and Community Health. By C. E. TURNER, A.M., Sc.D., DR.P.H., Professor of Public Health in the Massachusetts Institute of Technology; Formerly Associate Professor of Hygiene in the Tufts College Medical and Dental Schools; Sometime Member of the Administrative Board in the School of Public Health of Harvard University and the Massachusetts Institute of Technology. Seventh ed. Pp. 585; many figs., 4 colored plates. St. Louis: The C. V. Mosby Company, 1943. Price, $3.50.

A Textbook of Medicine. Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College; Attending Physician, New York Hospital; Visiting Physician, Bellevue Hospital, New York City. Associate Editor for "Diseases of the Nervous System;" and FOSTER KENNEDY, M.D., F.R.S.E., Professor of Clinical Neurology, Cornell University Medical College; Attending Physician, New York Hospital; Visiting Physician in Charge, Neurological Service, Bellevue Hospital; Consulting Physician, New York Neurological Institute. Sixth ed. Pp. 1566; 193 figs. Philadelphia and London: W. B. Saunders Company, 1943. Price, $9.50.

Textbook of Physiology. By WILLIAM D. ZOETHOUT, PH.D., Professor of Physiology in the Chicago College of Dental Surgery (Loyola University); and W. W. TUTTLE, PH.D., Professor of Physiology, College of Medicine, State University of Iowa. Eighth ed. Pp. 728; 308 text illus., 3 color plates. St. Louis: The C. V. Mosby Company, 1943. Price, $4.75.

This book is sufficiently in demand to appear in new editions every few years consequently its form shows a gradual progress without violent changes. In this edition some changes have been made in presentation and many of the figures have been redrawn. Some of the newer knowledge is incorporated but the scope of the book, which is written for students with little background, does not justify the use of such material on a large scale.   H. B.

China's Health Problems. By SZEMING SZE, General Secretary, Chinese Medical Association, Editor, Chinese Medical Journal. Pp. 60. Washington, D. C.: Chinese Medical Association (P. O. Box 6096), 1943. Price, $1.00.

Quantitative Pharmaceutical Chemistry. Containing Theory and Practice of Quantitative Analysis Applied to Pharmacy. By GLENN L. JENKINS, PH.D., Professor of Pharmaceutical Chemistry, College of Pharmacy, University of Minnesota; and ANDREW G. DUMEZ, PH.D., Professor of Pharmacy and Dean of the School of Pharmacy, University of Maryland. Second ed., 6th impression. Pp. 466; 67 figs.; 69 tables. New York and London: McGraw-Hill Book Company, Inc., 1937.

CORRECTIONS

In the June 1943 issue of this Journal, the article by Dr. C. P. Rhoads, C.T., Klopp and J. C. Abels entitled "The Relationship Between Riboflavin Intake and Thiamin Excretion in Man," should have had as its title—"The Relationship Between Thiamin Intake and Riboflavin Excretion in Man."

In the article on The Present Status of Contrast Myelography in the section "Radiology under the direction of Harry M. Weber, M.D., and David G. Pugh, M.D.," appearing in November issue, the author was wrongly given in the authors' manuscript as Dr. Weber instead of Dr. Pugh.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

NEW NOTICE TO CONTRIBUTORS AND SUBSCRIBERS

Activated by a directive from the War Production Board, we have changed the size of our type page for the "duration" to effect an economy in the amount of paper used. While there is a smaller number of pages, the amount of material has not been noticeably reduced.

We hope that any unpleasant effect produced by cutting down the margins will be accepted and approved by readers as a temporary war casualty. It is possible that more radical changes will have to be made later, but we are loath to change any more than absolutely necessary, a format that has existed practically unchanged since the Journal began in 1820.

For the balance of the war, 150 reprints will be supplied gratis. Covers will be omitted on all articles. In ordering additional reprints, we will supply in multiples of 150. This modification is for the same reason as the change of format, *i. e.,* conservation of paper.

NOTICE TO SUBSCRIBERS AND ADVERTISERS

We desire to secure several copies of the March and May 1943 numbers of this Journal, in order to comply with requests and need for replacements in long library "runs." The war situation has made it impossible to print extra numbers to supply this demand. We would be very grateful to anyone who would return to the Publishers any unmutilated copies of these numbers for which they have no further use, and we would be glad to repay postage.

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